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(54) Title: THERAPEUTIC PHOSPHONATE COMPOUNDS

(57) Abstract: The invention is related to phosphorus substituted therapeutic agents, compositions containing such phosphorus substituted agents, and therapeutic methods that include the administration of such phosphorus substituted agents, as well as to processes and intermediates useful for preparing such agents.



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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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THEAPEUTIC PHOSPHONATE COMPOUNDS

PRIORITY OF INVENTION

- 10 This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial Nos. 60/465630, 60/465400, 60/465587, 60/465728, 60/465601, 60/465463, 60/465602, 60/465639, 60/465593, 60/465546, 60/465472, 60/465473, 60/465598, 60/465633, 60/465550, 60/465610, 60/465720, 60/465634, 60/465537, 60/465698,
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60/513564, 60/513588, 60/514298, 60/514330, 60/514258, 60/514021,
60/514241, and 60/514299, all filed October 24, 2003; and to U.S. Provisional
Patent Application Serial No. 60/515266, all filed October 29, 2003; and to U.S.
10 Provisional Patent Application Serial No. 60/519476, filed November 12, 2003;
and to U.S. Provisional Patent Application Serial No. 60/524340, filed
November 20, 2003; and to U.S. Provisional Patent Application Serial Nos.
60/532257, 60/532230, 60/531960, 60/532160, 60/531940, 60/532273,
60/532184, 60/532183, 60/532274, and 60/531932, all filed December 22, 2003;
15 and to U.S. Provisional Patent Application Serial Nos. 60/532591, 60/532683,
60/532682, 60/532587, and 60/532415, all filed December 23, 2003; and to U.S.
Provisional Patent Application Serial Nos. 60/536003, 60/536007, 60/536027,
60/536006, 60/536180, 60/536005, 60/536179, 60/536054, 60/536004, and
60/536009, all filed January 12, 2004. The entirety of all Provisional
20 Applications listed above are incorporated herein by reference.

FIELD OF THE INVENTION

25 The invention relates generally to therapeutic phosphonate containing
compounds.

BACKGROUND OF THE INVENTION

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has

proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, *e.g.*, to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (*e.g.*, glucocorticoids and other anti-inflammatory drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, *e.g.*, blood/brain, epithelial, and cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract.

Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells.

Thus, there is a need for novel therapeutic agents, *e.g.* drugs, having improved therapeutic properties, pharmacokinetic properties, activity, oral bioavailability, potency, or effective half-lives *in vivo*. Such agents may also have distinct resistance profiles, fewer side effects, less complicated dosing schedules, or have increased oral activity.

25

SUMMARY OF THE INVENTION

Intracellular targeting may be achieved by methods and compositions that allow accumulation or retention of biologically active agents inside cells. The present invention provides novel phosphonate containing analogs of therapeutic compounds. These compounds possess the utilities of the related therapeutic compounds, but due to the presence of the phosphonate group(s) they typically provide cellular accumulation of the analog. Thus, compounds of the invention may demonstrate improved therapeutic properties, pharmacokinetic

properties, oral bioavailability, potency, or extended effective half-life *in vivo*, or a combination thereof. The compounds of the invention may also have distinct resistance profiles, fewer side effects, less complicated dosing schedules, or have increased oral activity.

5 The present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. The invention is more particularly related to attaining high concentrations of phosphonate-containing molecules in target cells. Such effective targeting may be applicable to a variety of therapeutic formulations and procedures.

10 Accordingly, in one embodiment the invention provides a compound of the invention which is a conjugate comprising an therapeutic compound linked to one or more phosphonate groups; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment the invention provides the use of a cell-
15 permeable conjugate comprising a therapeutic agent linked to one or more phosphonate groups, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for treating a disease or condition in a mammal, wherein after entry into cells, the cell-permeable conjugate is converted to a therapeutically active agent having reduced cell permeability.

20 In another embodiment the invention also provides a method for treating a disease or condition in a mammal, comprising administering to the mammal a therapeutically effective amount of a cell-permeable conjugate comprising a therapeutic agent linked to one or more phosphonate groups, or a pharmaceutically acceptable salt or solvate thereof, wherein, following
25 administration, the cell-permeable conjugate enters cells of the mammal and therein is converted to a therapeutically active agent having reduced cell permeability.

The invention also provides a pharmaceutical composition comprising an effective amount of a conjugate of the invention, or a pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable excipient.

This invention also pertains to a method of increasing cellular accumulation and retention of a therapeutic drug compound comprising linking the compound to one or more phosphonate groups.

The invention also provides processes and novel intermediates disclosed 5 herein which are useful for preparing conjugates of the invention. Some of the compounds of the invention are useful to prepare other compounds of the invention.

DETAILED DESCRIPTION

10 Reference will now be made in detail to certain claims of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated claims, it will be understood that they are not intended to limit the invention to those claims. On the contrary, the invention is intended to cover all alternatives, 15 modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein 20 are intended to have the following meanings:

When tradenames are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

“Bioavailability” is the degree to which the pharmaceutically active agent 25 becomes available to the target tissue after the agent's introduction into the body. Enhancement of the bioavailability of a pharmaceutically active agent can provide a more efficient and effective treatment for patients because, for a given dose, more of the pharmaceutically active agent will be available at the targeted tissue sites.

30 The terms “phosphonate” and “phosphonate group” include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to a heteroatom , 3) single-bonded

- to a heteroatom, and 4) single-bonded to another heteroatom, wherein each heteroatom can be the same or different. The terms "phosphonate" and "phosphonate group" also include functional groups or moieties that comprise a phosphorous in the same oxidation state as the phosphorous described above, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having the characteristics described above. For example, the terms "phosphonate" and "phosphonate group" include phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamide, and phosphonthioate functional groups.
- 10 In one specific embodiment of the invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen, and 4) single-bonded to another oxygen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteristics. In another specific embodiment of the invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen or nitrogen, and 4) single-bonded to another oxygen or nitrogen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteristics.
- 15 20

The term "cell-permeable conjugate" includes conjugates that have the ability to pass through cell walls either actively or passively, for example, by diffusion or by active transport. The cell permeable conjugate may or may not have therapeutic activity itself. According to certain aspects of the invention, a cell-permeable conjugate enters into cells, wherein it is converted to an agent having therapeutic activity and reduced cell permeability. This conversion can occur by any suitable mechanism, such as, for example, by hydrolysis or by the action of one or more enzymes as described herein below. The term "agent having reduced cell permeability" as used herein includes agents that have a

reduced cell permeability compared to the corresponding cell permeable conjugate that enters the cells. In one embodiment, the agent having reduced cell permeability has about 2 times less cell permeability than the corresponding cell permeable conjugate; in another embodiment, the agent having reduced cell permeability has about 3 times less cell permeability than the corresponding cell permeable conjugate; in another embodiment, the agent having reduced cell permeability has about 5 times less cell permeability than the corresponding cell permeable conjugate; and in another embodiment, the agent having reduced cell permeability has about 10 times less cell permeability than the corresponding cell permeable conjugate.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, *i.e.* active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Prodrug moiety" refers to a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^9$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^9$ where R^9 is $\text{C}_1\text{--C}_6$ alkyl, $\text{C}_1\text{--C}_6$ substituted alkyl, $\text{C}_6\text{--C}_{20}$ aryl or $\text{C}_6\text{--C}_{20}$ substituted aryl. The acyloxyalkyl ester was first used as a prodrug

strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (De Lombaert et al. (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g., esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al. (1992) *J. Chem. Soc. Perkin Trans. II* 2345; Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide.

Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al. (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al. (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al., US Patent No. 6312662).

“Protecting group” refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g., Protective Groups in Organic Chemistry*, 10 Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of 15 the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, 20 optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of 25 the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after 30 deprotection, *e.g.*, alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium),

- 5 an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is $\text{C}_1\text{-C}_4$ alkyl). Physiologically acceptable salts of a compound having an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, 10 benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound having a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a $\text{C}_1\text{-C}_4$ alkyl group).

- 15 For therapeutic use, salts of active ingredients of the compounds of the invention will typically be physiologically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable 20 compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

- “Alkyl” is $\text{C}_1\text{-C}_{18}$ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me , - CH_3), ethyl (Et , - CH_2CH_3), 1-propyl ($\underline{\text{n}}\text{-Pr}$, $\underline{\text{n}}\text{-propyl}$, - $\text{CH}_2\text{CH}_2\text{CH}_3$), 2-propyl (i-Pr , i-propyl , - $\text{CH}(\text{CH}_3)_2$), 1-butyl ($\underline{\text{n}}\text{-Bu}$, $\underline{\text{n}}\text{-butyl}$, - $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-methyl-1-propyl (j-Bu , j-butyl , - $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2-butyl (s-Bu , s-butyl , - $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 2-methyl-2-propyl (t-Bu , t-butyl , - $\text{C}(\text{CH}_3)_3$), 1-pentyl ($\underline{\text{n}}\text{-pentyl}$, - $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-pentyl (- $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$), 3-pentyl (- $\text{CH}(\text{CH}_2\text{CH}_3)_2$), 2-methyl-2-butyl (- $\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$), 3-methyl-2-butyl (- $\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 3-methyl-1-butyl (- $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2-methyl-1-butyl (- $\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1-hexyl (- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-hexyl (- $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3-

hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃).

“Alkenyl” is C₂-C₁₈ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp*² double bond. Examples include, but are not limited to, ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), 5-hexenyl (-CH₂CH₂CH₂CH=CH₂), and 2,5-hexadienyl (-CH₂CH=CHCH₂CH=CH₂).

“Alkynyl” is C₂-C₁₈ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. Examples include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH₂C≡CH), and 2,5-hexadiynyl (-CH₂C≡CH CH₂C≡CH)

“Alkylene” refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to, methylene (-CH₂-), 1,2-ethyl (-CH₂CH₂-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

“Alkenylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

“Alkynylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but

are not limited to, acetylene (-C≡C-), propargyl (-CH₂C≡C-), and 4-pentynyl (-CH₂CH₂CH₂C≡CH-).

“Aryl” means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a 5 parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

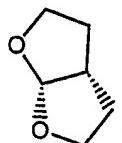
“Arylalkyl” refers to an acyclic alkyl radical in which one of the 10 hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, , naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g., the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the 15 aryl moiety is 5 to 14 carbon atoms.

“Substituted alkyl”, “substituted aryl”, and “substituted arylalkyl” mean 20 alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R, -O⁻, -OR, -SR, -S⁻, -NR₂, -NR₃, =NR, -CX₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N₂, -N₃, NC(=O)R, -C(=O)R, -C(=O)NRR, -S(=O)₂O⁻, -S(=O)₂OH, -S(=O)₂R, -OS(=O)₂OR, -S(=O)₂NR, -S(=O)R, -OP(=O)O₂RR, -P(=O)O₂RR, -P(=O)(O⁻)₂, -P(=O)(OH)₂, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, -C(O)O⁻, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is 25 independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

“Heterocycle” as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of 30 Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs” (John Wiley & Sons, New York, 1950 to present), in

particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (e.g. 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (e.g. O, N, or S).

- 5 Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, 10 piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, 15 isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoazinyl, isochromanyl, chromanyl, 20 imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



- By way of example and not limitation, carbon bonded heterocycles can 25 be bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 30 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8

of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles can be bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrrolidine, 3-pyrrolidine, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, 10 indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetidyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

“Carbocycle” refers to a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicyclic, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles typically have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. 15 Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

The term “chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

The term “stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

30 “Diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling

points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

“Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term “treatment” or “treating,” to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PG groups do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for

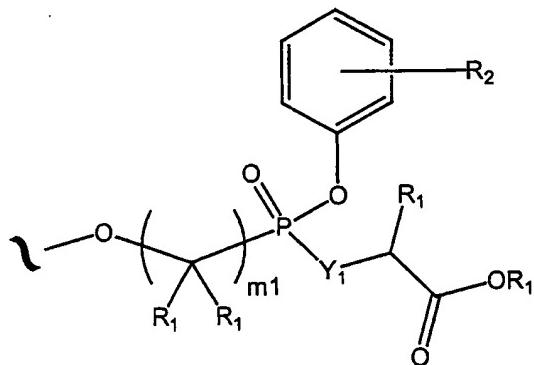
carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

5 Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

10 The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, *i.e.* they may or may be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

15 Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997) and are included within the scope of the present invention. An exemplary phosphonate ester-forming group is the phenyl carbocycle in substructure A₃, having the formula:

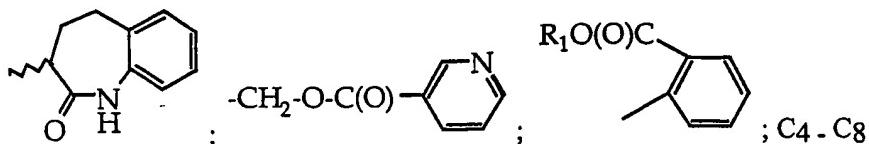


wherein R₁ may be H or C₁-C₁₂ alkyl; m₁ is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R₂ groups. Where Y₁ is O, a lactate ester is formed, and where Y₁ is N(R₂), N(OR₂) or N(N(R₂)₂), a phosphonamidate ester results.

In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in $-CO_2R^x$ where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

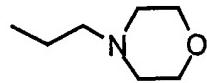
- 5 Examples of protecting groups include:
C₃-C₁₂ heterocycle (described above) or aryl. These aromatic groups
optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2-
and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3-
and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-
pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,
10 C₃-C₁₂ heterocycle or aryl substituted with halo, R¹, R¹-O-C₁-C₁₂
alkylene, C₁-C₁₂ alkoxy, CN, NO₂, OH, carboxy, carboxyester, thiol, thioester,
C₁-C₁₂ haloalkyl (1-6 halogen atoms), C₂-C₁₂ alkenyl or C₂-C₁₂ alkynyl. Such
groups include 2-, 3- and 4-alkoxyphenyl (C₁-C₁₂ alkyl), 2-, 3- and 4-
15 methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-
diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-
hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-
hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl,
2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3-
20 and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and
3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl,
2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4-
and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-,
3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 4-
25 trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-,
3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 4-
trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-
trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-
ethylpiperazinyl, benzyl, alkylsalicylphenyl (C₁-C₄ alkyl, including 2-, 3- and 4-
30 ethylsalicylphenyl), 2,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl (-C₁₀H₆-
OH) and aryloxy ethyl [C₆-C₉ aryl (including phenoxy ethyl)], 2,2'-

dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -C₆H₄CH₂-N(CH₃)₂, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C₁₋₄ alkyl);



esters of 2-carboxyphenyl; and C₁-C₄ alkylene-C₃-C₆ aryl (including benzyl, -

- 5 CH₂-pyrrolyl, -CH₂-thienyl, -CH₂-imidazolyl, -CH₂-oxazolyl, -CH₂-isoxazolyl, -CH₂-thiazolyl, -CH₂-isothiazolyl, -CH₂-pyrazolyl, -CH₂-pyridinyl and -CH₂-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C₁-C₁₂ alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C₁-C₁₂ haloalkyl (1 to 6 halogen atoms; including -
- 10 CH₂CCl₃), C₁-C₁₂ alkyl (including methyl and ethyl), C₂-C₁₂ alkenyl or C₂-C₁₂ alkynyl; alkoxy ethyl [C₁-C₆ alkyl including -CH₂-CH₂-O-CH₃ (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including -CH₃, -CH(CH₃)₂, -C(CH₃)₃, -CH₂CH₃, -(CH₂)₂CH₃, -(CH₂)₃CH₃, -(CH₂)₄CH₃, -(CH₂)₅CH₃, -CH₂CH₂F, -



- 15 CH₂CH₂Cl, -CH₂CF₃, and -CH₂CCl₃); -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH₂-C(O)-N(R¹)₂, -CH₂-S(O)(R¹), -CH₂-S(O)₂(R¹), -CH₂-CH(OC(O)CH₂R¹)-CH₂(OC(O)CH₂R¹), cholesteryl, enolpyruvate (HOOC-C(=CH₂)-), glycerol; a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9

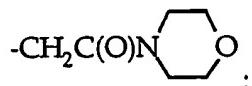
- 20 monosaccharide residues); triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C₆₋₂₆, C₆₋₁₈ or C₆₋₁₀ fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.*

(1974) 5(6):670-671;

- 5 cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters
 (Sakamoto et al., *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R₁,
 R₄ or aryl; and



10 The hydroxyl groups of the compounds of this invention optionally are
 substituted with one of groups III, IV or V disclosed in WO 94/21604, or with
 isopropyl.

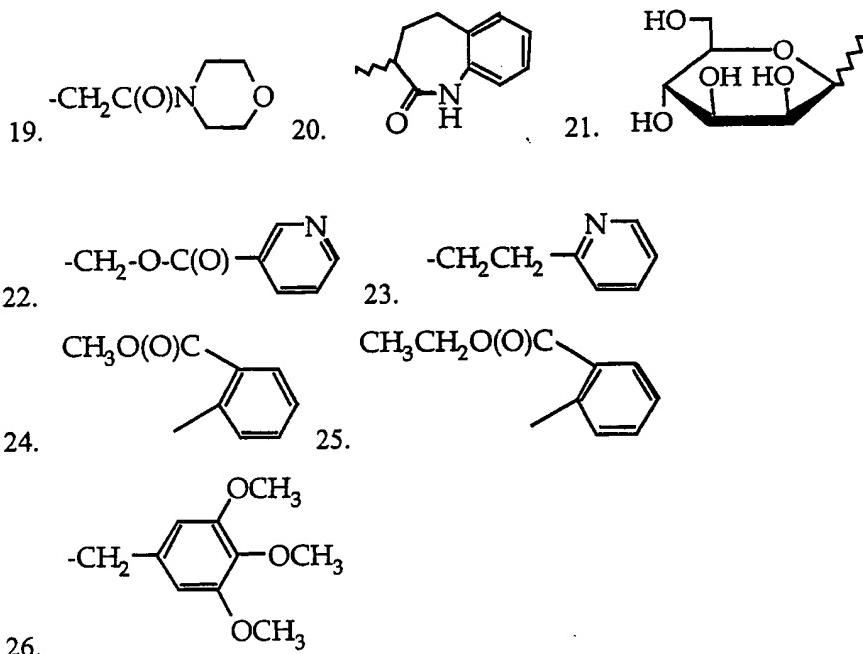
- 15 Table A lists examples of protecting group ester moieties that for example
 can be bonded via oxygen to -C(O)O- and -P(O)(O-)₂ groups. Several amides
 also are shown, which are bound directly to -C(O)- or -P(O)2. Esters of
 structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound
 herein having a free hydroxyl with the corresponding halide (chloride or acyl
 chloride and the like) and N,N-dicyclohexyl-N-morpholine carboxamidine (or
 another base such as DBU, triethylamine, CsCO₃, N,N-dimethylaniline and the
 like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone).
- 20 When the compound to be protected is a phosphonate, the esters of structures 5-7,
 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt
 (or the corresponding amines in the case of compounds such as 13, 14 and 15)
 with the monochlorophosphonate or dichlorophosphonate (or another activated
 phosphonate).

25

TABLE A

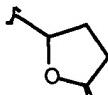
1. -CH ₂ -C(O)-N(R ₁) ₂ *	10. -CH ₂ -O-C(O)-C(CH ₃) ₃
2. -CH ₂ -S(O)(R ₁)	11. -CH ₂ -CCl ₃
3. -CH ₂ -S(O) ₂ (R ₁)	12. -C ₆ H ₅
30 4. -CH ₂ -O-C(O)-CH ₂ -C ₆ H ₅	13. -NH-CH ₂ -C(O)O-CH ₂ CH ₃
5. 3-cholesteryl	14. -N(CH ₃)-CH ₂ -C(O)O-CH ₂ CH ₃

6. 3-pyridyl
 7. N-ethylmorpholino
 8. -CH₂-O-C(O)-C₆H₅
 9. -CH₂-O-C(O)-CH₂CH₃
15. -NHR₁
 16. -CH₂-O-C(O)-C₁₀H₁₅
 17. -CH₂-O-C(O)-CH(CH₃)₂
 18. -CH₂-C#H(OC(O)CH₂R₁)-CH₂-
 -(OC(O)CH₂R₁)*
- 5



- chiral center is (R), (S) or racemate.

- Other esters that are suitable for use herein are described in EP 632048.
 15 Protecting groups also includes "double ester" forming profunctionalities

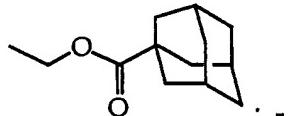


such as -CH₂OC(O)OCH₃, -CH₂SCCOCH₃, -CH₂OCON(CH₃)₂, or alkyl- or aryl-acyloxyalkyl groups of the structure -CH(R¹ or W⁵)O((CO)R³⁷) or -CH(R¹ or W⁵)((CO)OR³⁸) (linked to oxygen of the acidic group) wherein R³⁷ and R³⁸ are alkyl, aryl, or alkylaryl groups (see U.S. Patent No. 4968788).

- 20 Frequently R³⁷ and R³⁸ are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including

normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including -

- 5 CH(CH₂CH₂OCH₃)OC(O)C(CH₃)₃,



; -

CH₂OC(O)C₁₀H₁₅, -CH₂OC(O)C(CH₃)₃, -CH(CH₂OCH₃)OC(O)C(CH₃)₃, -

CH(CH(CH₃)₂)OC(O)C(CH₃)₃, -CH₂OC(O)CH₂CH(CH₃)₂, -

CH₂OC(O)C₆H₁₁, -CH₂OC(O)C₆H₅, -CH₂OC(O)C₁₀H₁₅, -

CH₂OC(O)CH₂CH₃, -CH₂OC(O)CH(CH₃)₂, -CH₂OC(O)C(CH₃)₃ and -

- 10 CH₂OC(O)CH₂C₆H₅.

In some claims the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other claims, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are

- 15 found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that 20 such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical

- 25 ester groups are defined at least on WO 95/07920 pages 89-93 (under R³¹ or R³⁵), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C₁-C₄ alkylestercarboxyphenyl 30 (salicylate C₁-C₁₂ alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds 5 of the invention having protected groups, in particular amino acid amides or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is 10 employed, e.g., the esters may be different or the same, or a mixed amide and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates. For example:

- 15 • Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenylloxymethyl, Siloxymethyl, 2-
- 20 Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyran-3-yl, 3-Bromotetrahydropyran-1-yl, Tetrahydrothiopyran-1-yl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyran-1-yl, 4-Methoxytetrahydrothiopyran-1-yl, 4-Methoxytetrahydropyran-1-yl, 4-[2-Chloro-4-methyl]phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuran-2-yl, Tetrahydrothiofuran-2-yl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));
- 25 • Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,
- 30 • *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);

- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picoly N-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberyl,
- 5 Triphenylmethyl, α -Naphthylidiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoyloxyphenyl)methyl, 4,4',4"-Tris(benzoxyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzoisothiazolyl *S,S*-Dioxido);
- Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylhexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);
- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- 25 • Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);
- 30 • Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-

(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate);
 Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-
 4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-
 dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate,

- 5 Monosuccinate, (*E*)-2-Methyl-2-butenoate (Tiglate), *o*-
 (Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α -Naphthoate, Nitrate, Alkyl
 N,N,N',N' -Tetramethylphosphorodiamidate, *N*-Phenylcarbamate, Borate,
 Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and
 • Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate,
 10 Tosylate).

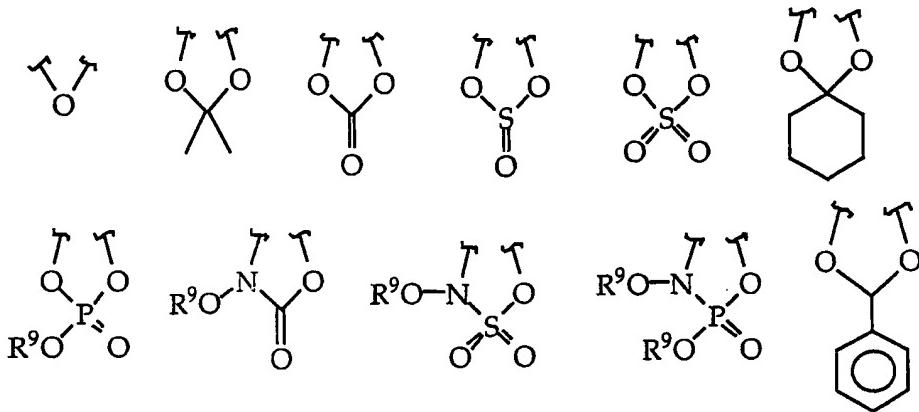
Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-

t-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-

- 15 Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene,
 Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-
 Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic
 Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-
 Methoxyethylidene, 1-Ethoxyethylidene, 1,2-Dimethoxyethylidene, α -
 20 Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-
 Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl
 Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-
 Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene),
 Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

- 25 More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C1-C6 alkyl.

Amino protecting groups

- 5 Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:
- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
 - Substituted Ethyl: (2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);
 - 15 • Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-

acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);

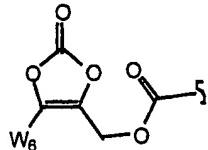
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p*'-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);
- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);
- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzoyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);
- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-

triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);

- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolyamine *N*⁺-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N*,*N*-dimethylaminomethylene, *N*,*N*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);
- *N*-*N* Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- *N*-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- *N*-Si Derivatives, *N*-S Derivatives, and *N*-Sulfonyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobzenenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilylyethanesulfonyl, *N*-9-

anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, -NHC(O)R¹ or -N=CR¹N(R¹)₂. Another protecting group, 5 also useful as a prodrug for amino or -NH(R⁵), is:



See for example Alexander, J. et al. (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the 10 invention has the structure R¹⁵NHCH(R¹⁶)C(O)-, where R¹⁵ is H, an amino acid or polypeptide residue, or R⁵, and R¹⁶ is defined below.

R¹⁶ is lower alkyl or lower alkyl (C₁-C₆) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C₆-C₇ aryl, guanidinyl, imidazolyl, indolyl, sulphydryl, sulfoxide, and/or alkylphosphate. R¹⁰ also is taken together 15 with the amino acid α-N to form a proline residue (R¹⁰ = -CH₂)₃-). However, R¹⁰ is generally the side group of a naturally-occurring amino acid such as H, -CH₃, -CH(CH₃)₂, -CH₂-CH(CH₃)₂, -CHCH₃-CH₂-CH₃, -CH₂-C₆H₅, -CH₂CH₂-S-CH₃, -CH₂OH, -CH(OH)-CH₃, -CH₂-SH, -CH₂-C₆H₄OH, -CH₂-CO-NH₂, -CH₂-CH₂-CO-NH₂, -CH₂-COOH, -CH₂-CH₂-COOH, -(CH₂)₄-NH₂ and - 20 (CH₂)₃-NH-C(NH₂)-NH₂. R₁₀ also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, -NHSO₂R, NHC(O)R, -N(R)₂, NH₂ or -NH(R)(H), whereby for example 25 a carboxylic acid is reacted, *i.e.* coupled, with the amine to form an amide, as in C(O)NR₂. A phosphonic acid may be reacted with the amine to form a phosphonamide, as in -P(O)(OR)(NR₂).

In general, amino acids have the structure R¹⁷C(O)CH(R¹⁶)NH-, where R¹⁷ is -OH, -OR, an amino acid or a polypeptide residue. Amino acids are low

molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group.

Generally the amino acids will be found in nature, *i.e.*, can be detected in biological material such as bacteria or other microbes, plants, animals or man.

- 5 Suitable amino acids typically are alpha amino acids, *i.e.* compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono- or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues
10 contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulphydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof.

- 15 Polypeptides most typically will be substantially composed of such naturally- occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally,
20 unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene- encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general
25 review, see Spatola, A. F., in Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

- When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R³ of substituents A¹, A² or A³ in a compound
30 of the invention. These conjugates are produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Similarly, conjugates are formed between and an

amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R³ is amidated with an 5 amino acid. In general, the α -amino or α -carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, *i.e.*, carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the 10 conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, *e.g.*, by R¹, esterified with R⁵ or amidated. Similarly, the amino side chains R¹⁶ optionally will be blocked with R¹ or substituted with R⁵.

15 Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The 20 esters or amino acid or polypeptide amides also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

25 When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are 30 useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more

efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

5 Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β -hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β -methylaspartic acid, β -methylglutamic acid, β , β -dimethylaspartic acid, γ -hydroxyglutamic acid, β , γ -dihydroxyglutamic acid, β -phenylglutamic acid, γ -methyleneglutamic acid, 3-amino adipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

10 Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyric acid, ornithine, citrulline, homoarginine, homocitrulline, hydroxylysine, allohydroxylysine and diaminobutyric acid;

15 Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α , α' -diaminosuccinic acid, α , α' -diaminogluutaric acid, α , α' -diamino adipic acid, α , α' -diaminopimelic acid, α , α' -diamino- β -hydroxypimelic acid, α , α' -diaminosuberic acid, α , α' -diaminoazelaic acid, and α , α' -diaminosebacic acid;

20 Imino acids such as proline, hydroxyproline, allohydroxyproline, γ -methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C₁-C₈ branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α -methylserine, α -amino- α -methyl- γ -hydroxyvaleric acid, α -amino- α -methyl- δ -hydroxyvaleric acid, α -amino- α -methyl- ϵ -hydroxycaproic acid, isovaline, α -methylglutamic acid, α -aminoisobutyric acid, α -aminodiethylacetic acid, α -aminodiisopropylacetic acid, α -aminodi-n-propylacetic acid, α -aminodiisobutylacetic acid, α -aminodi-n-butylacetic acid, α -aminoethylisopropylacetic acid, α -amino-n-propylacetic acid, α -aminodiisoamyacetic acid, α -methylaspartic acid, α -methylglutamic acid, 1-

aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert*-leucine, β -methyltryptophan and α -amino- β -ethyl- β -phenylpropionic acid; β -phenylserinyl;

Aliphatic α -amino- β -hydroxy acids such as serine, β -hydroxyleucine, β -hydroxynorleucine, β -hydroxynorvaline, and α -amino- β -hydroxystearic acid;

5 α -Amino, α -, γ -, δ - or ϵ -hydroxy acids such as homoserine, δ -hydroxynorvaline, γ -hydroxynorvaline and ϵ -hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

10 2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α -Amino- β -thiols such as penicillamine, β -thiolnorvaline or β -thiolbutyryne;

Other sulfur containing amino acid residues including cysteine; homocystine, β -phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

15 Phenylalanine, tryptophan and ring-substituted α -amino acids such as the phenyl- or cyclohexylamino acids α -aminophenylacetic acid, α -aminocyclohexylacetic acid and α -amino- β -cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy,

20 guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, o-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-

25 hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α -Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α -Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

30 Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next

amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial 5 proteins. They include enzymes (*e.g.*, hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amides are useful as immunogens in raising antibodies 10 against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis 15 or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically 20 used to raise antibodies, *e.g.*, rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic 25 heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, *e.g.*, a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are 30 specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is

covalently bonded through its α -amino group to the phosphorus or carbon atoms of the compounds herein. In claims where W₁ is phosphonate it is expected that this peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the 5 phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, PC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NK, NN, ND, NC, NE, NQ, NG, NH, NI, NL, 10 NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, 15 QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, 20 KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, 25 SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, 30 VS, VT, VW, VY and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence -X⁴-pro-X⁵- (where X⁴ is any amino

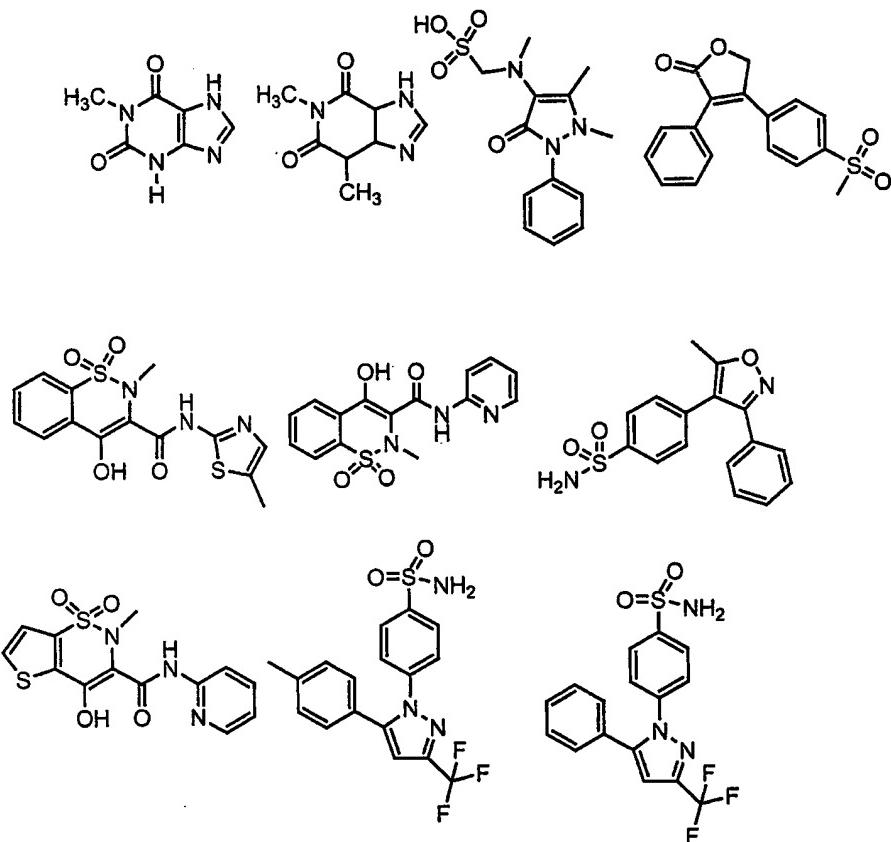
acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X^4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with 5 benzyl.

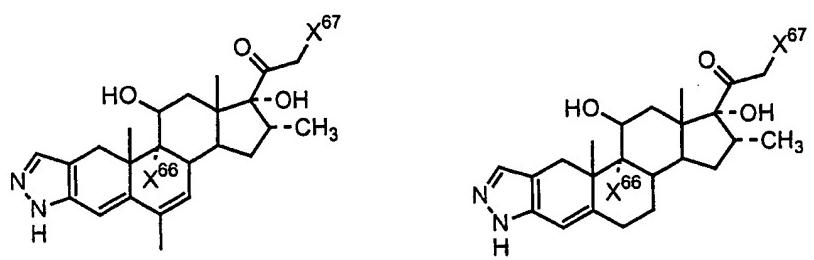
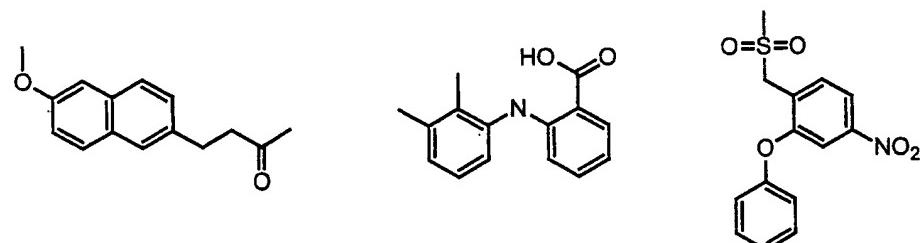
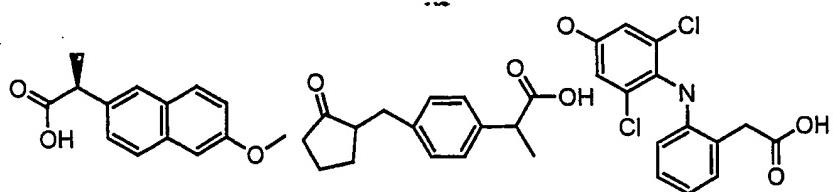
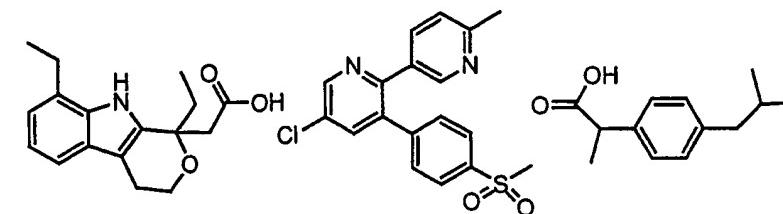
Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α -amino group are transport substrates for the peptide transporter found in brush 10 border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978). Transport competent peptides can thus be used to enhance bioavailability of the amide compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amide compounds of this invention. Amino acids in 15 the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor 20 substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase, and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also be applied to the selection 25 of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amides are immunogens or are useful for bonding to proteins in order to prepare immunogens.

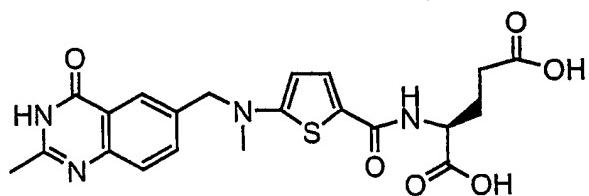
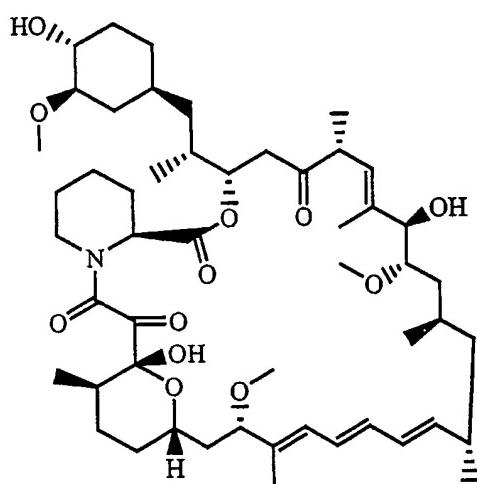
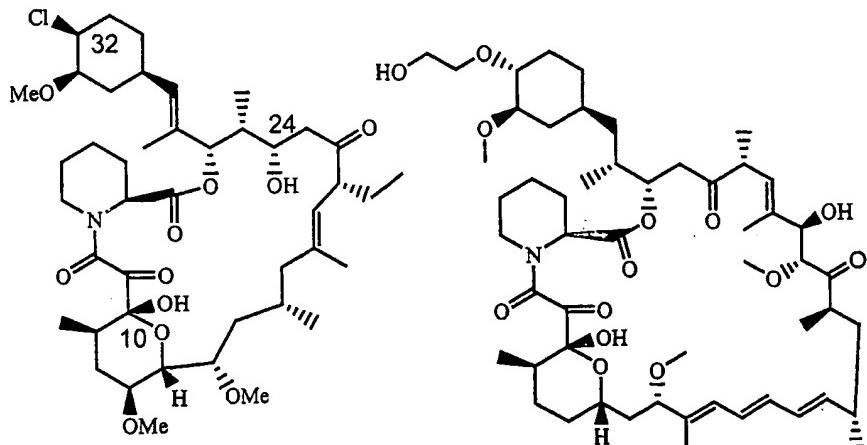
30 Specific Embodiments of the Invention

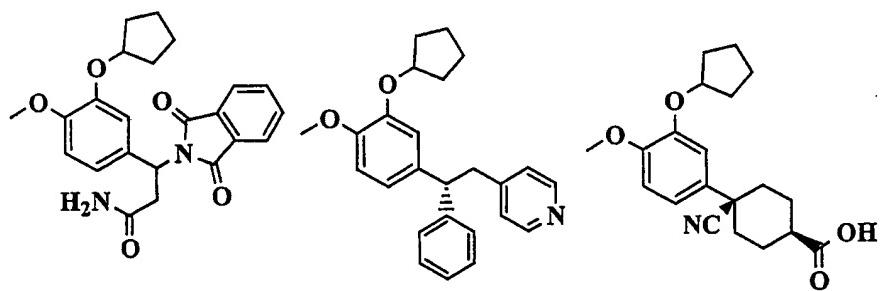
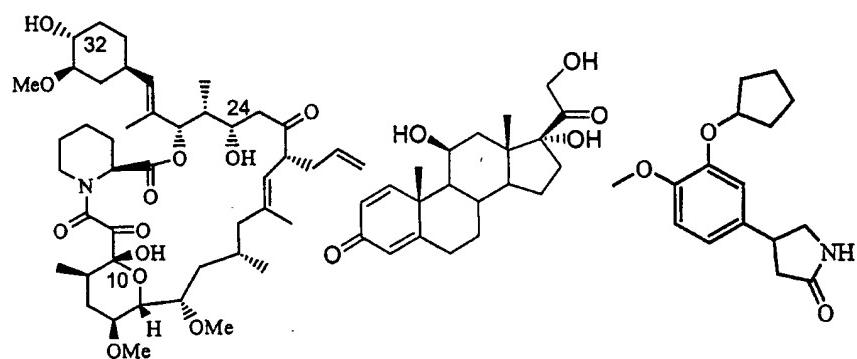
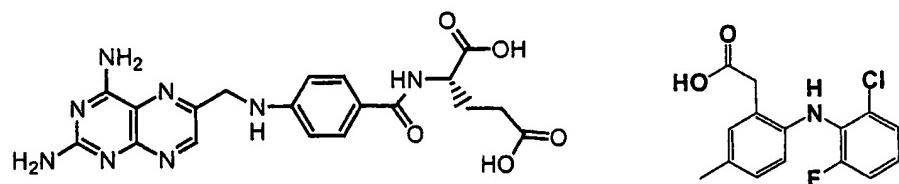
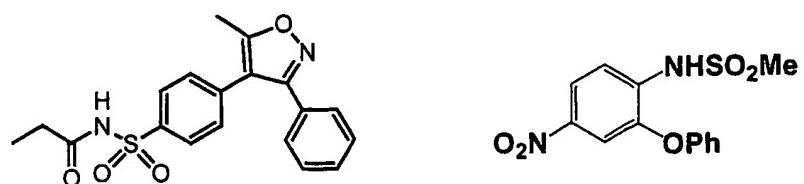
Specific values described for radicals, substituents, and ranges, as well as specific embodiments of the invention described herein, are for illustration only; they do not exclude other defined values or other values within defined ranges.

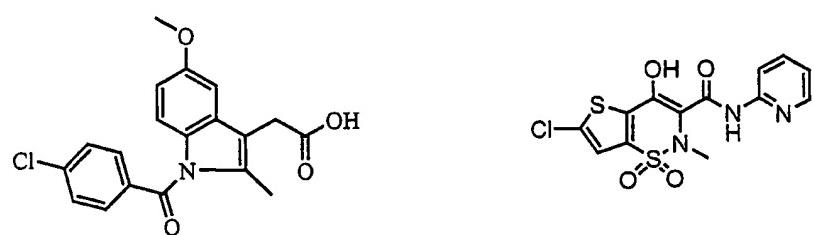
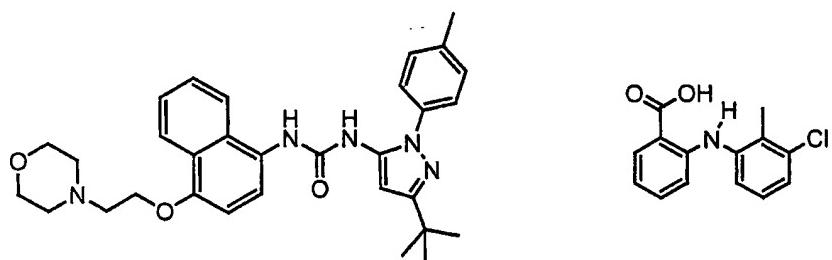
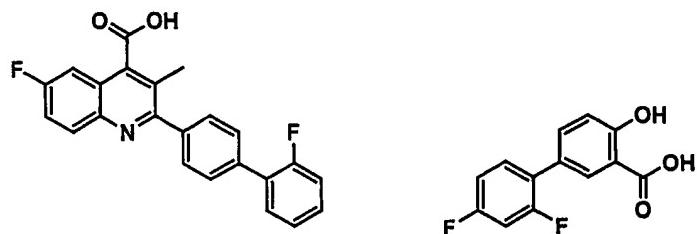
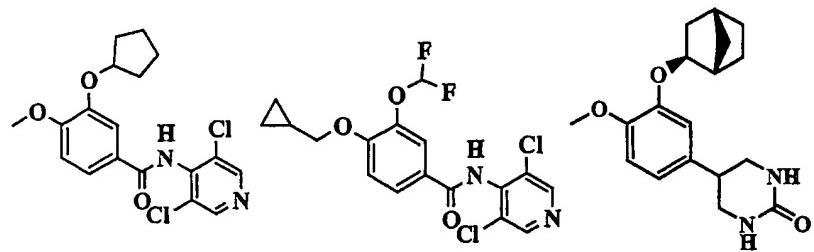
In one specific embodiment the invention provides a conjugate, or a
5 pharmaceutically acceptable salt or solvate thereof, that is a compound of any
one of the following formulae:

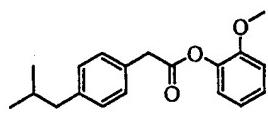
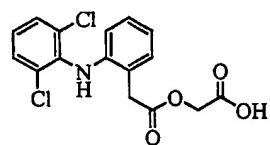
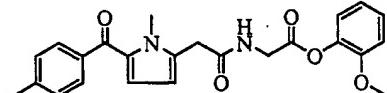
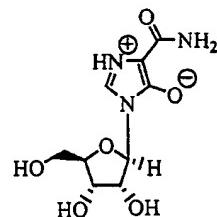
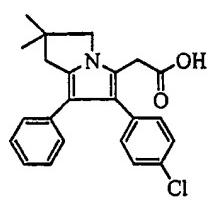
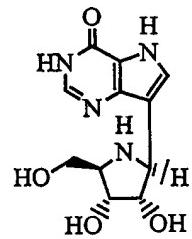
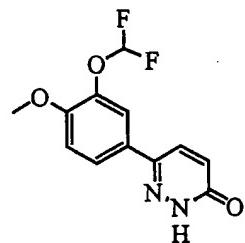
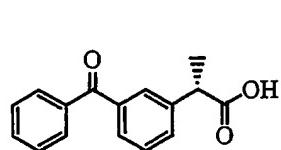
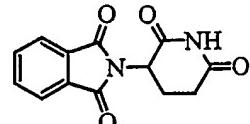
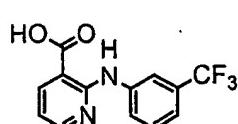
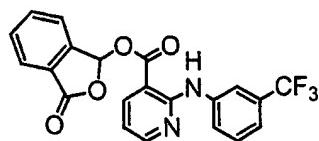
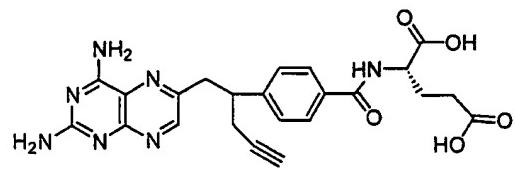
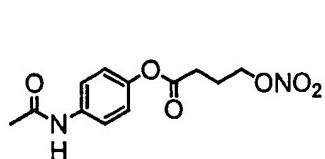


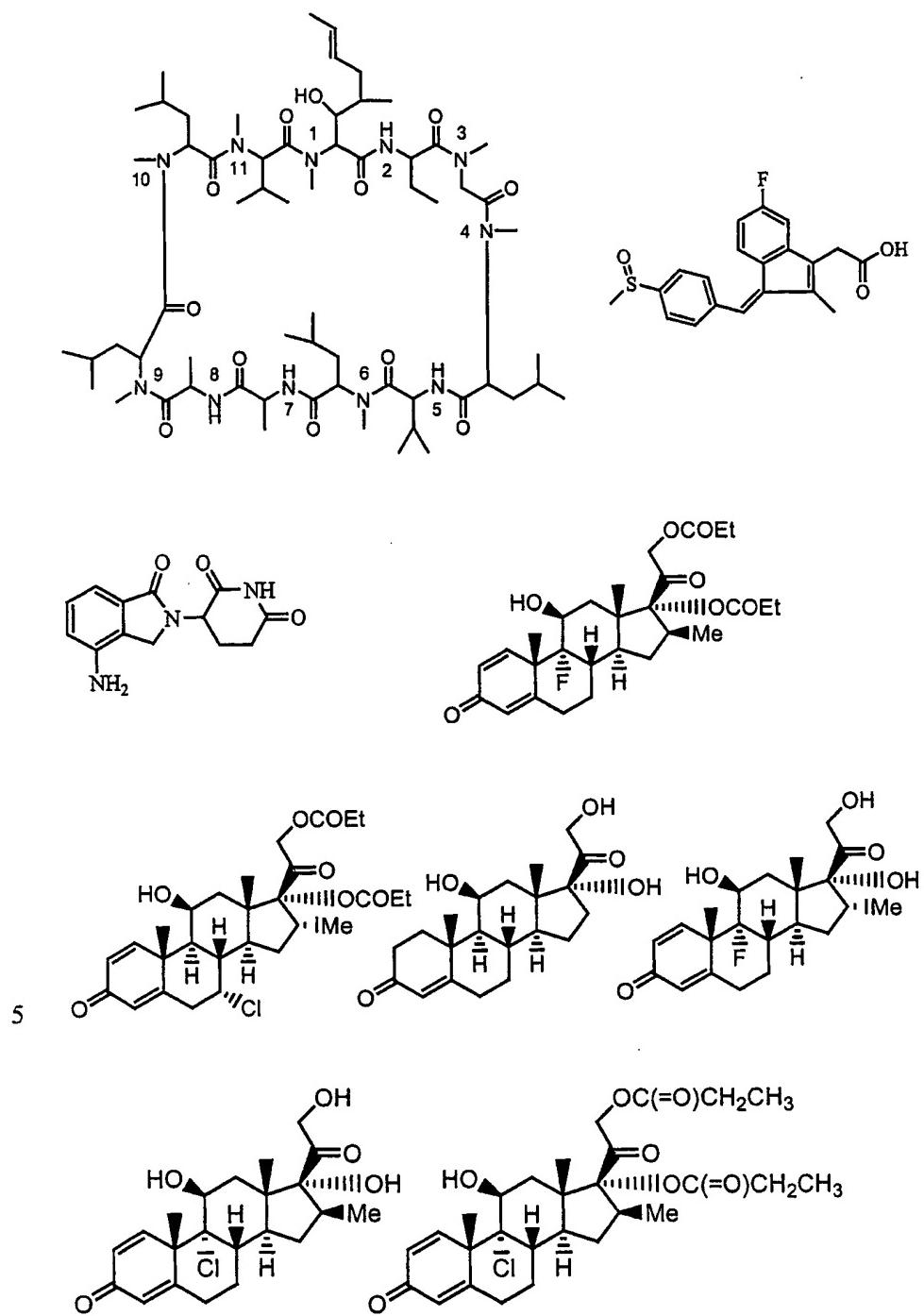


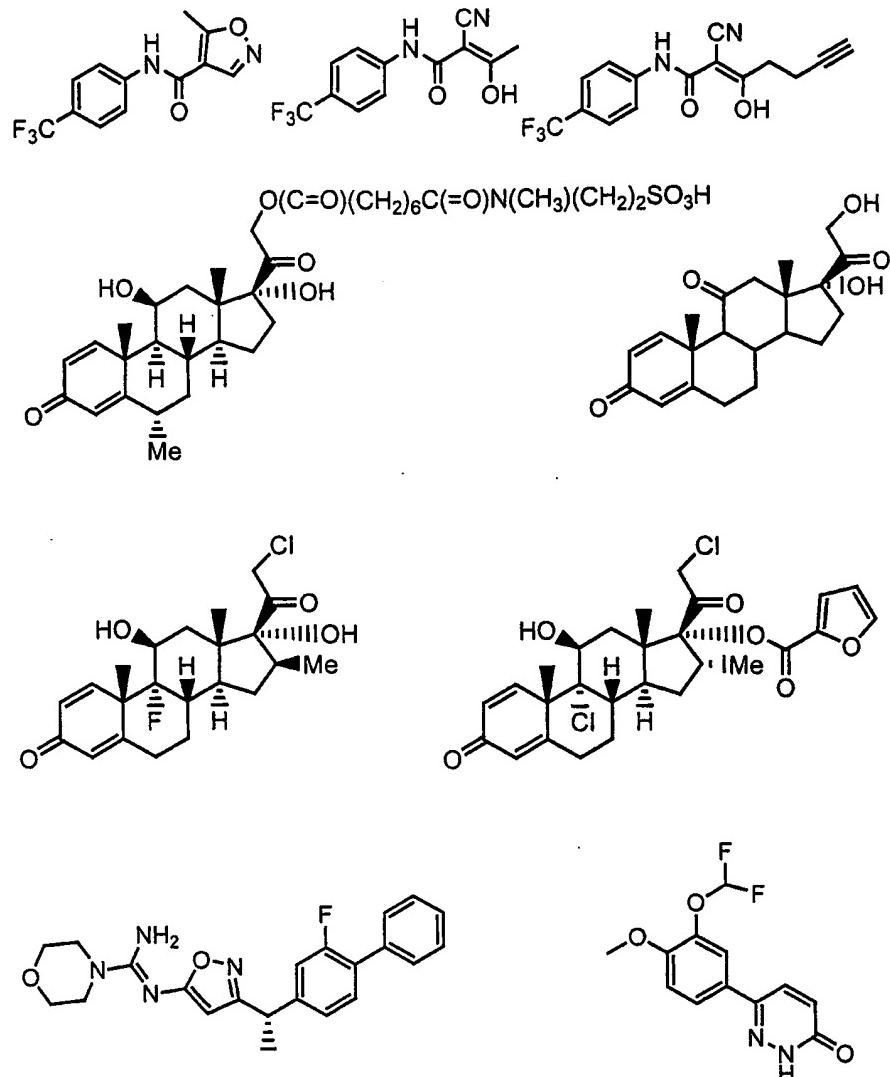




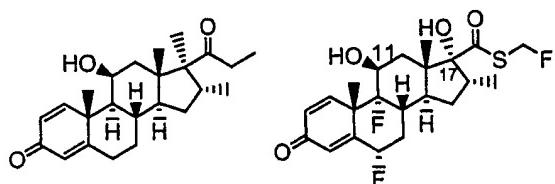
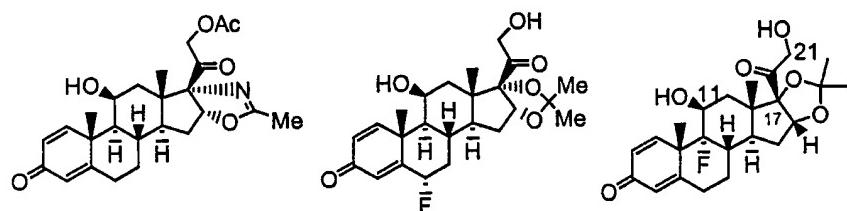
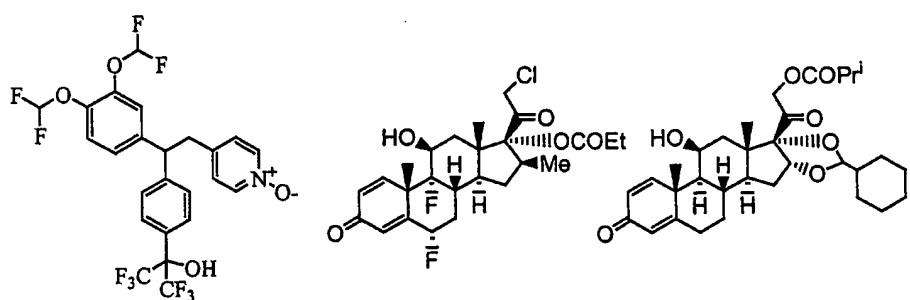
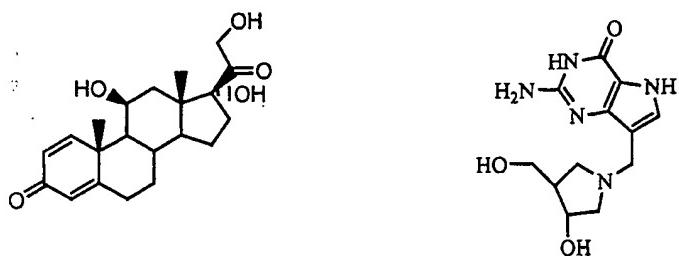
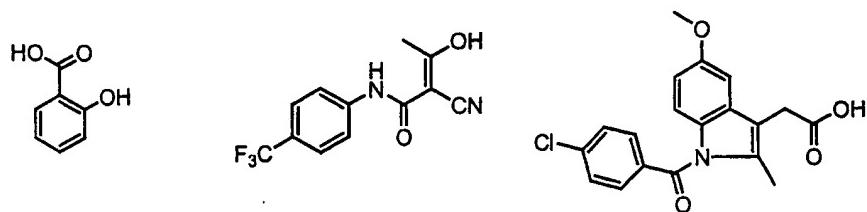


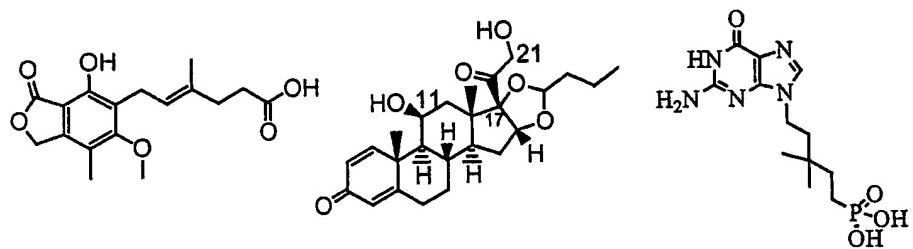
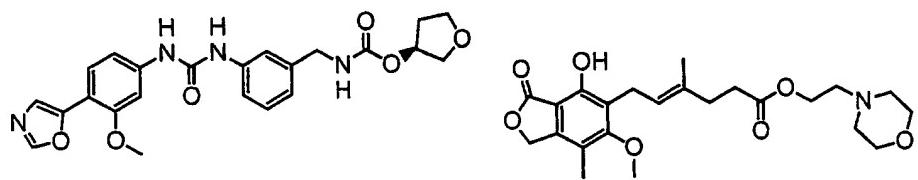
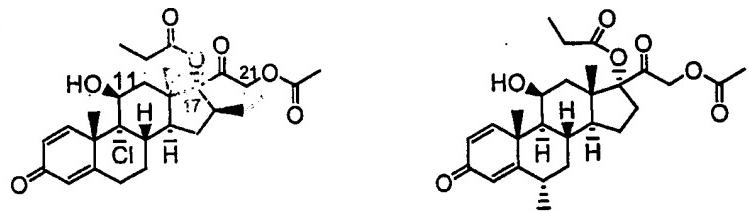
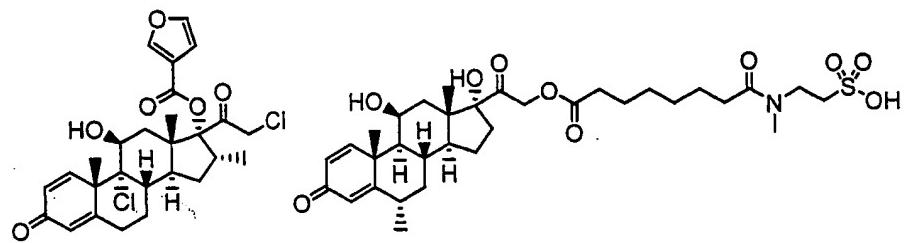


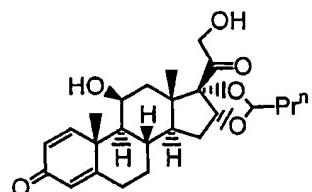
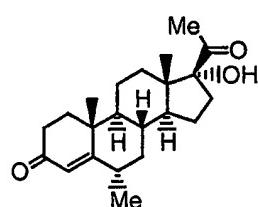
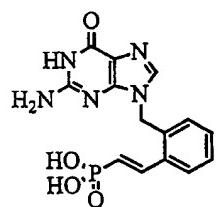
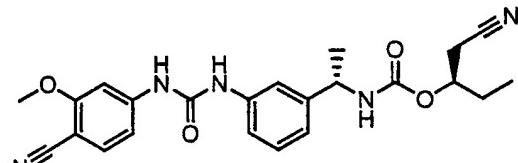
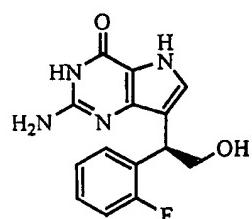
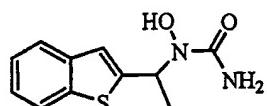
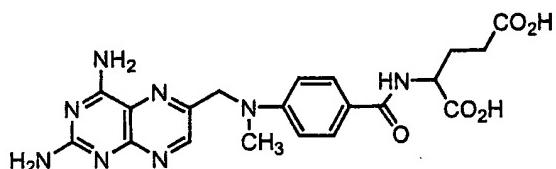
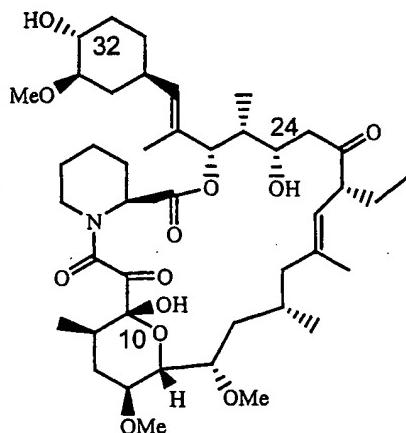
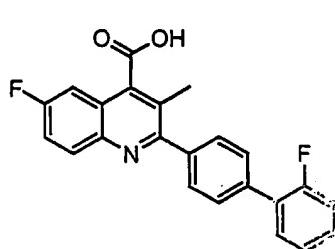




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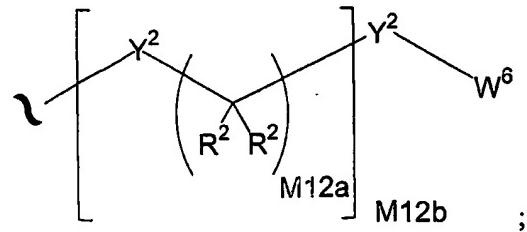
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that is substituted with one or more groups A^0 , wherein:

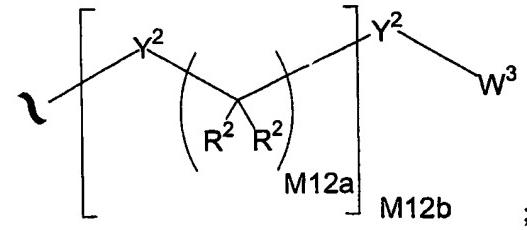
A^0 is A^1 , A^2 or W^3 with the proviso that the conjugate includes at least one A^1 ;

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A^1 is:

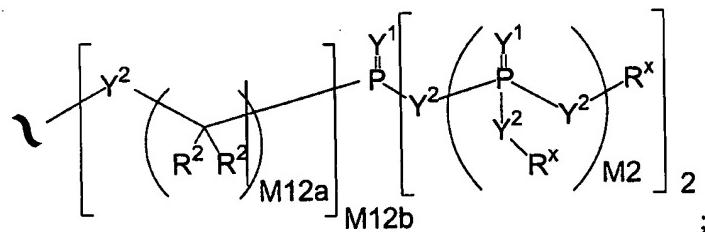


A² is:



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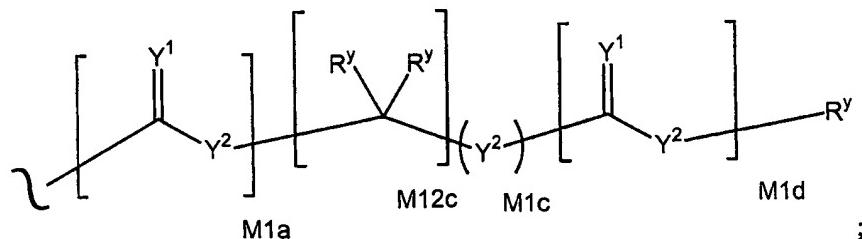
A³ is:



Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x))(R^x);

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x),
10 N(N(R^x))(R^x)), -S(O)_{M2}- , or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two
phosphorous atoms Y² can also be C(R²)(R²);

R^x is independently H, R¹, R², W³, a protecting group, or the formula:



wherein:

15 R^y is independently H, W³, R² or a protecting group;

R¹ is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1 , R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

5 R^3 is R^{3a} , R^{3b} , R^{3c} or R^{3d} , provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d} ;

R^{3a} is F, Cl, Br, I, -CN, N₃ or -NO₂;

R^{3b} is Y¹;

R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)₂R^x, -S(O)(OR^x), -

10 S(O)₂(OR^x), -OC(Y¹)R^x, -OC(Y¹)OR^x, -OC(Y¹)(N(R^x)(R^x)), -SC(Y¹)R^x, -SC(Y¹)OR^x, -SC(Y¹)(N(R^x)(R^x)), -N(R^x)C(Y¹)R^x, -N(R^x)C(Y¹)OR^x, or -N(R^x)C(Y¹)(N(R^x)(R^x)) ;

R^{3d} is -C(Y¹)R^x, -C(Y¹)OR^x or -C(Y¹)(N(R^x)(R^x));

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms,

15 or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5 ;

W^4 is R^5 , -C(Y¹)R⁵, -C(Y¹)W⁵, -SO_{M2}R⁵, or -SO_{M2}W⁵;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted

20 with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

 M2 is 0, 1 or 2;

 M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

 M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

25 M1a, M1c, and M1d are independently 0 or 1;

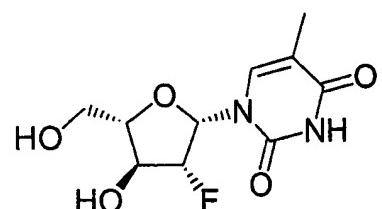
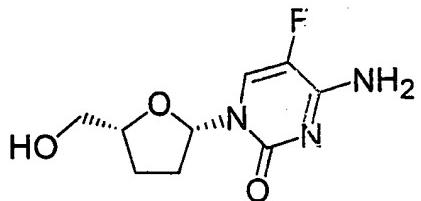
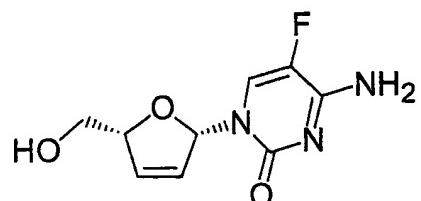
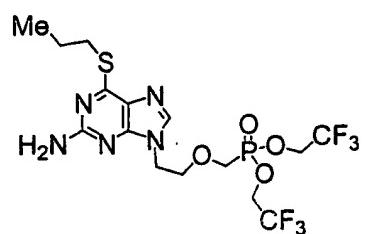
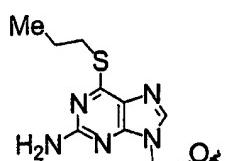
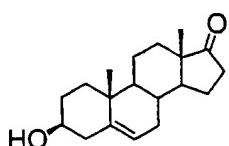
 M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

 X⁶⁶ is hydrogen or fluorine; and

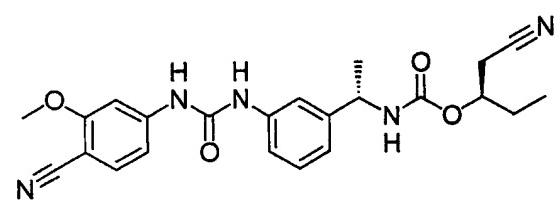
 X⁶⁷ is hydrogen, hydroxy, or acyloxy.

 In another embodiment the invention provides a conjugate, or a

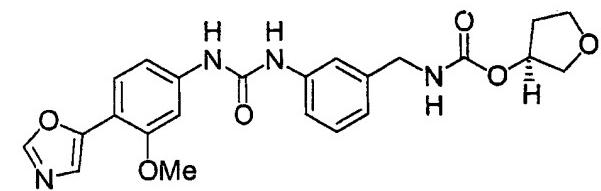
30 pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of the following formulae:

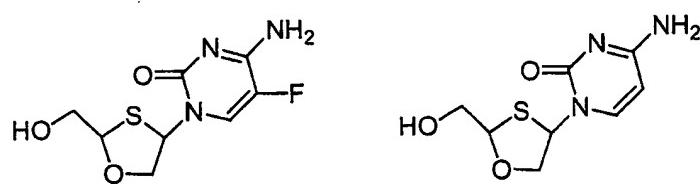
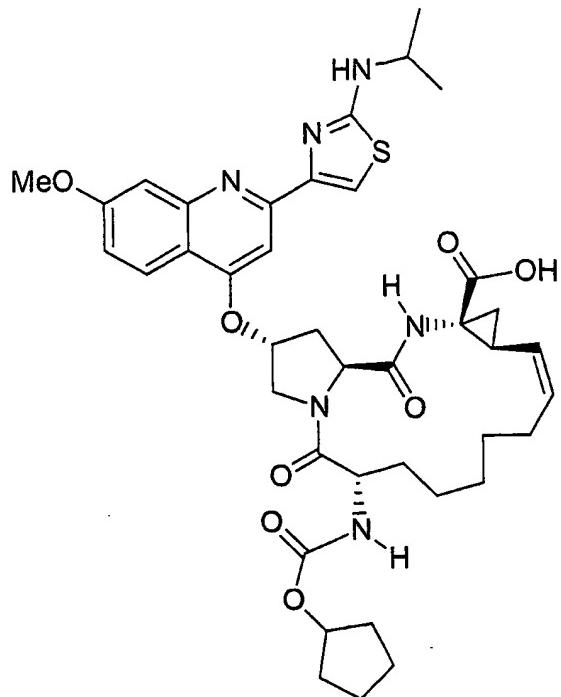


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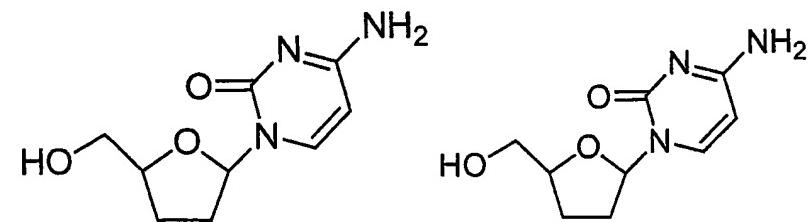
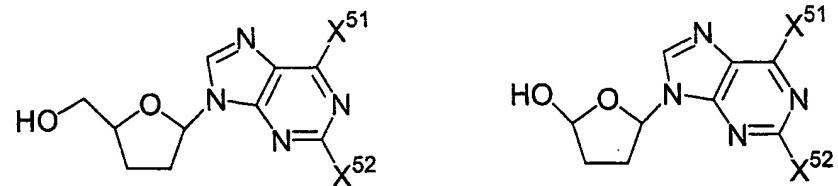


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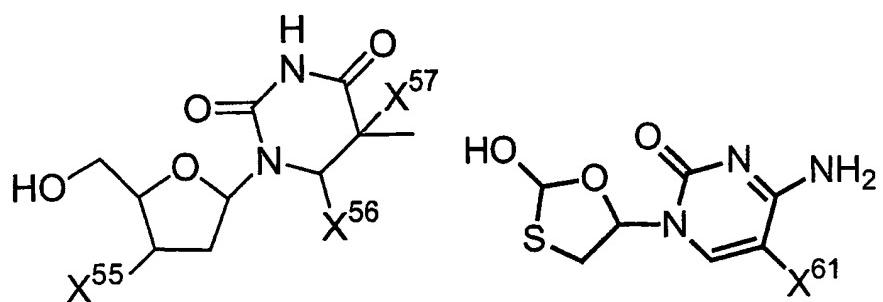
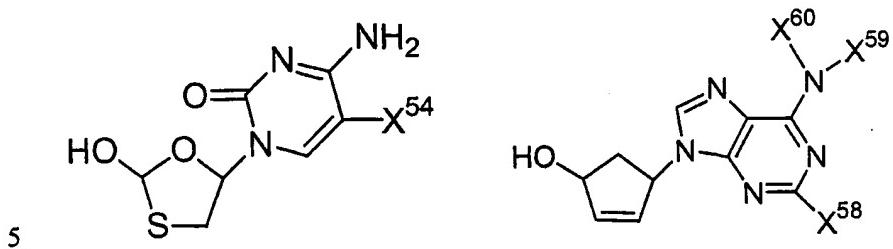
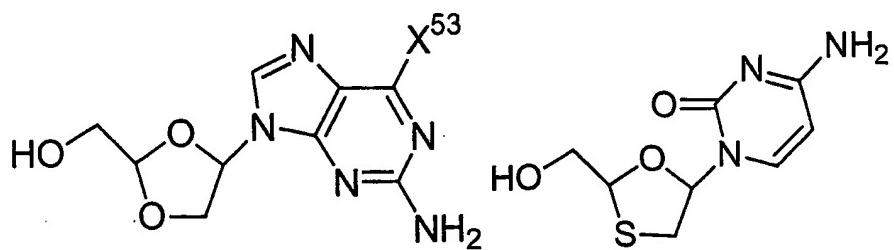


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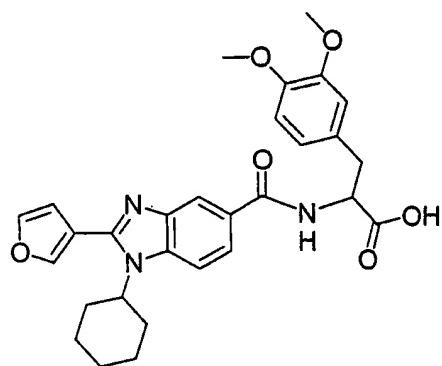


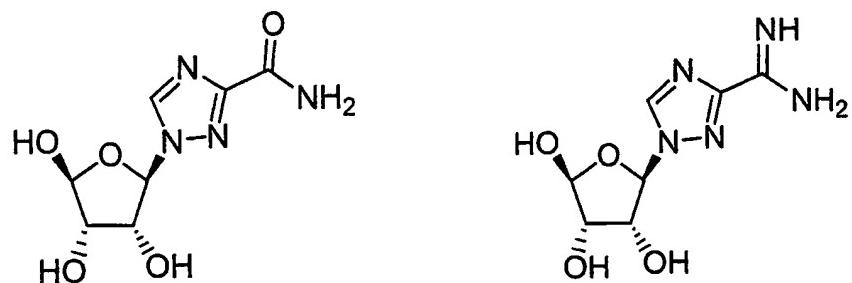
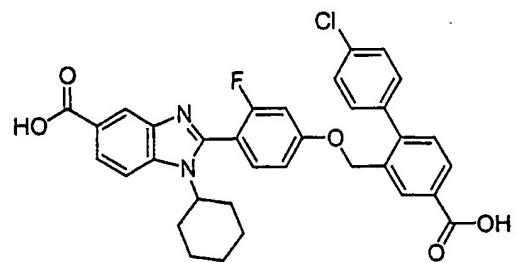
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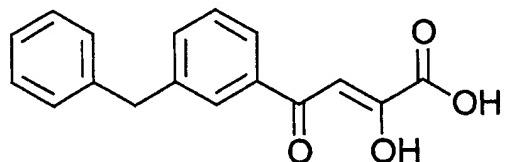
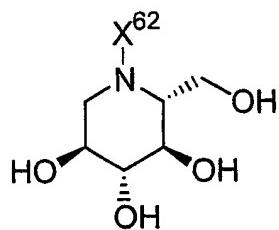
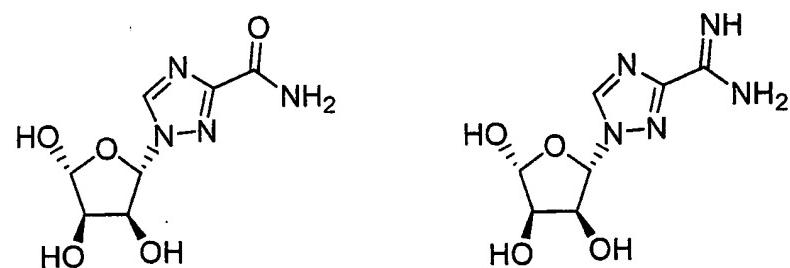


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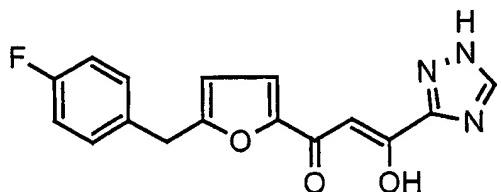




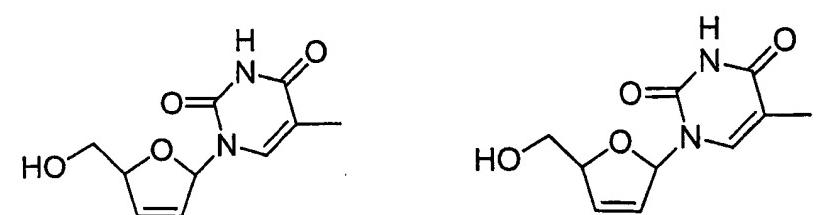
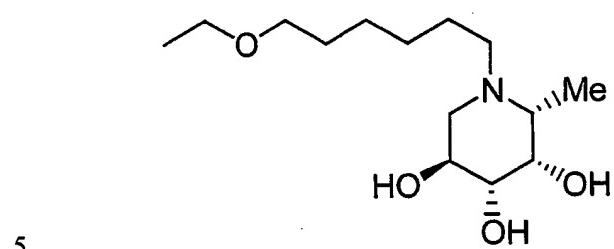
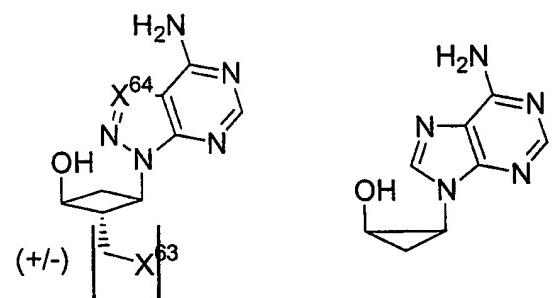
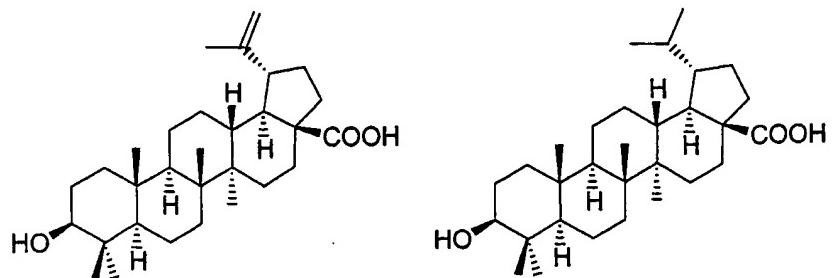
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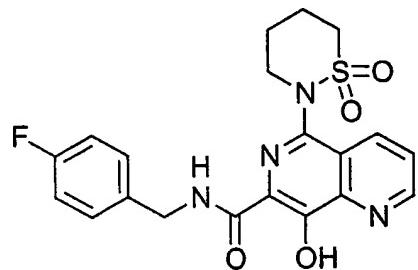
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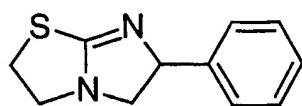
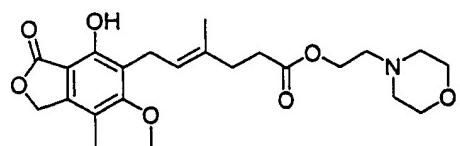
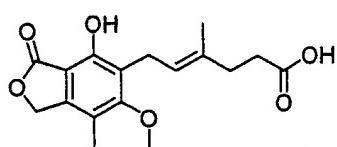


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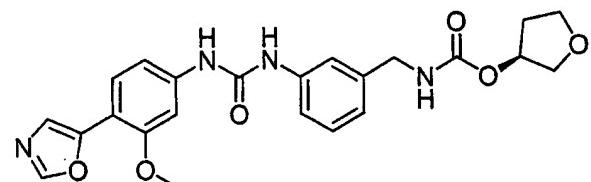
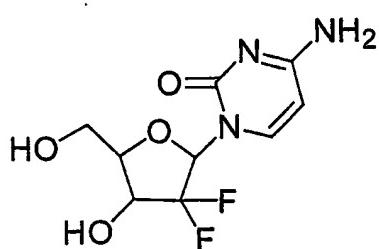
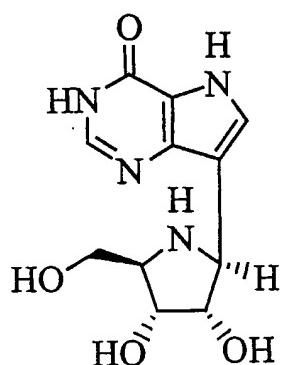


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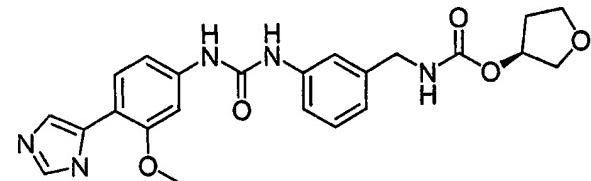




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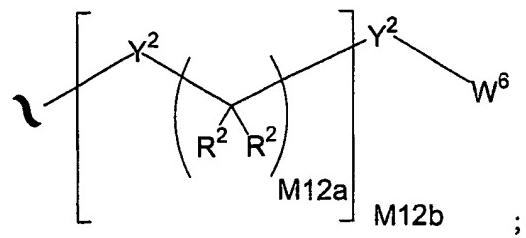
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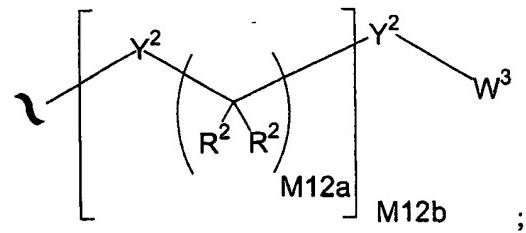
15 that is substituted with one or more groups A^0 , wherein:

A^0 is A^1 , A^2 or W^3 with the proviso that the conjugate includes at least one A^1 ;

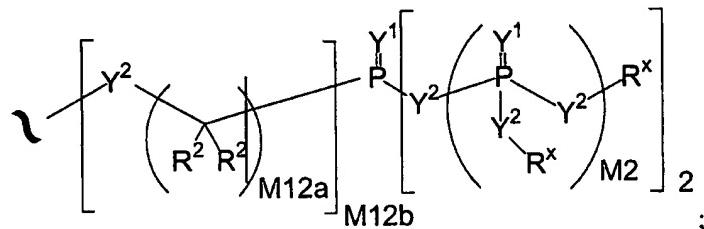
A^1 is:



A² is:



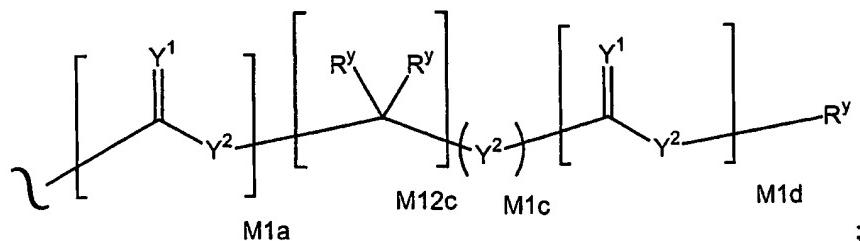
5 A³ is:



Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)), -S(O)_{M2}- , or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two phosphorous atoms Y² can also be C(R²)(R²);

R^x is independently H, R¹, R², W³, a protecting group, or the formula:



wherein:

15 R^y is independently H, W³, R² or a protecting group;

R¹ is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1 , R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

5 R^3 is R^{3a} , R^{3b} , R^{3c} or R^{3d} , provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d} ;

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1 ;

10 R^{3c} is $-R^X$, $-N(R^X)(R^X)$, $-SR^X$, $-S(O)R^X$, $-S(O)_2R^X$, $-S(O)(OR^X)$, $-S(O)_2(OR^X)$, $-OC(Y^1)R^X$, $-OC(Y^1)OR^X$, $-OC(Y^1)(N(R^X)(R^X))$, $-SC(Y^1)R^X$, $-SC(Y^1)OR^X$, $-SC(Y^1)(N(R^X)(R^X))$, $-N(R^X)C(Y^1)R^X$, $-N(R^X)C(Y^1)OR^X$, or $-N(R^X)C(Y^1)(N(R^X)(R^X))$;

R^{3d} is $-C(Y^1)R^X$, $-C(Y^1)OR^X$ or $-C(Y^1)(N(R^X)(R^X))$;

15 R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5 ;

W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

20 W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

$M2$ is 0, 1 or 2;

$M12a$ is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

$M12b$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

25 $M1a$, $M1c$, and $M1d$ are independently 0 or 1;

$M12c$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

X^{51} is OH, Cl, NH_2 , H, Me, or MeO;

X^{52} is H or NH_2 ;

X^{53} is OH, Cl, NH_2 , or H;

30 X^{54} is H or F;

X^{55} is H, N_3 , NH_2 , or $NHAc$;

X^{56} is alkyloxy, aryloxy, haloalkyloxy, alkenyloxy, aralyloxy;

X⁵⁷ is a halo;

X⁵⁸ is H, NH₂, or NH-alkyl;

X⁵⁹ and X⁶⁰ are independently H, alkyl, or cyclopropyl;

X⁶¹ is H or F;

5 X⁶² is H or alkyl of 1 to 18 carbon atoms;

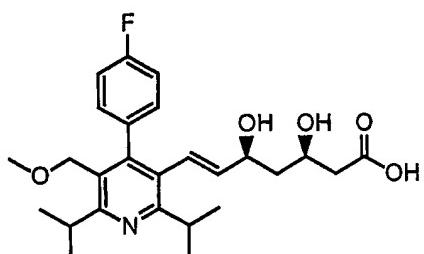
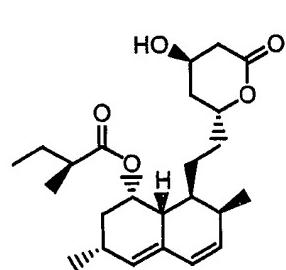
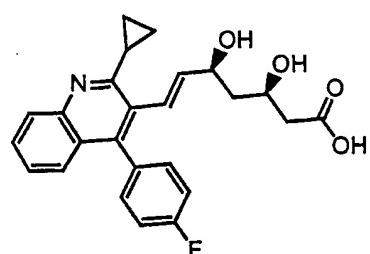
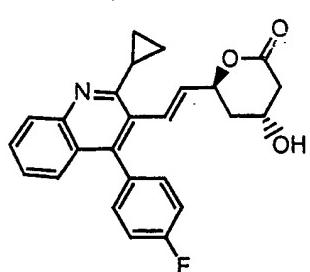
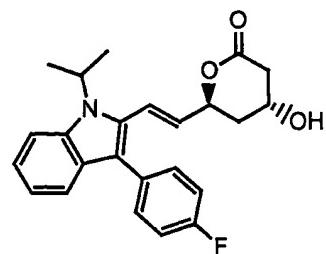
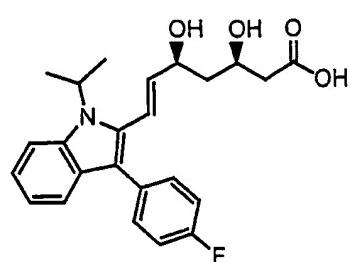
X⁶³ is OH, F, or cyano; and

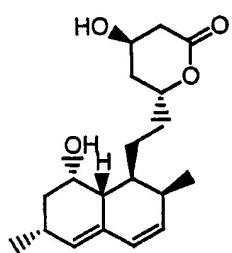
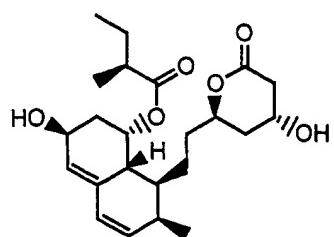
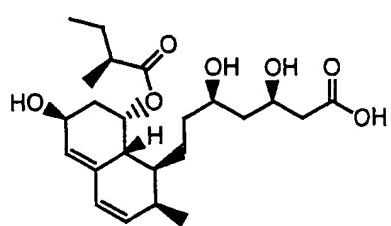
X⁶⁴ is N or CH.

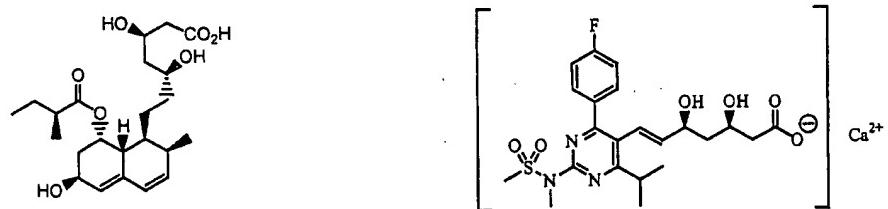
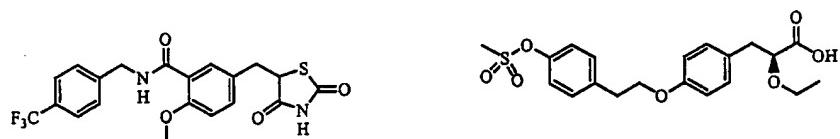
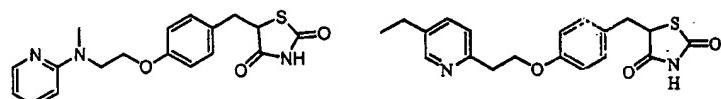
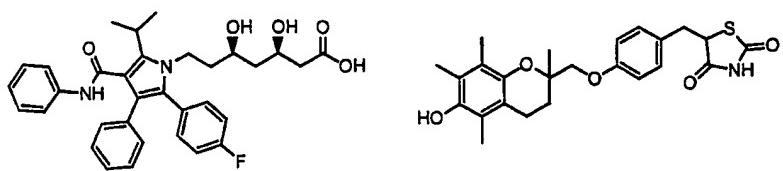
In another embodiment the invention provides a conjugate, or a

pharmaceutically acceptable salt or solvate thereof, that is a compound of any

10 one of the following formulae:





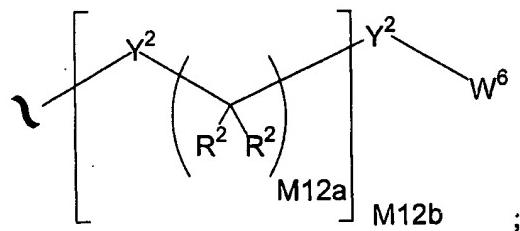
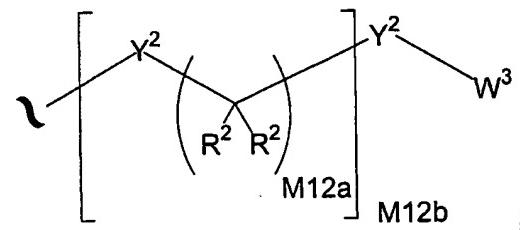
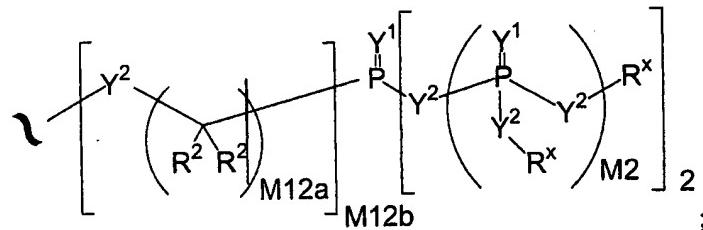


that is substituted with one or more groups A⁰, wherein:

A⁰ is A¹, A² or W³ with the proviso that the conjugate includes at least

5 one A¹;

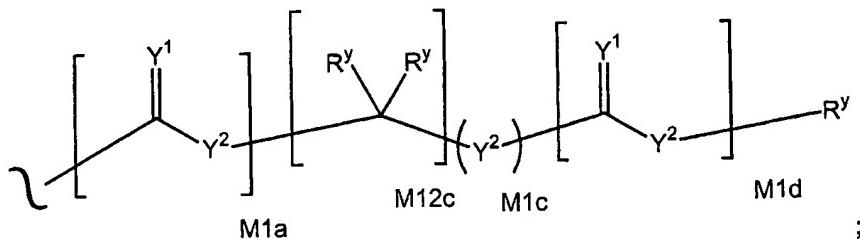
A¹ is:

A² is:5 A³ is:

Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x),
10 N(N(R^x)(R^x)), -S(O)M2-, or -S(O)M2-S(O)M2-; and when Y² joins two
phosphorous atoms Y² can also be C(R²)(R²);

R^x is independently H, R¹, R², W³, a protecting group, or the formula:



wherein:

15 R^y is independently H, W³, R² or a protecting group;

R¹ is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1 , R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

5 R^3 is R^{3a} , R^{3b} , R^{3c} or R^{3d} , provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d} ;

R^{3a} is F, Cl, Br, I, -CN, N₃ or -NO₂;

R^{3b} is Y¹;

R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)₂R^x, -S(O)(OR^x), -

10 S(O)₂(OR^x), -OC(Y¹)R^x, -OC(Y¹)OR^x, -OC(Y¹)(N(R^x)(R^x)), -SC(Y¹)R^x, -SC(Y¹)OR^x, -SC(Y¹)(N(R^x)(R^x)), -N(R^x)C(Y¹)R^x, -N(R^x)C(Y¹)OR^x, or -N(R^x)C(Y¹)(N(R^x)(R^x));

R^{3d} is -C(Y¹)R^x, -C(Y¹)OR^x or -C(Y¹)(N(R^x)(R^x));

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms,

15 or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5 ;

W^4 is R^5 , -C(Y¹)R⁵, -C(Y¹)W⁵, -SO_{M2}R⁵, or -SO_{M2}W⁵;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted

20 with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

 M2 is 0, 1 or 2;

 M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

 M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

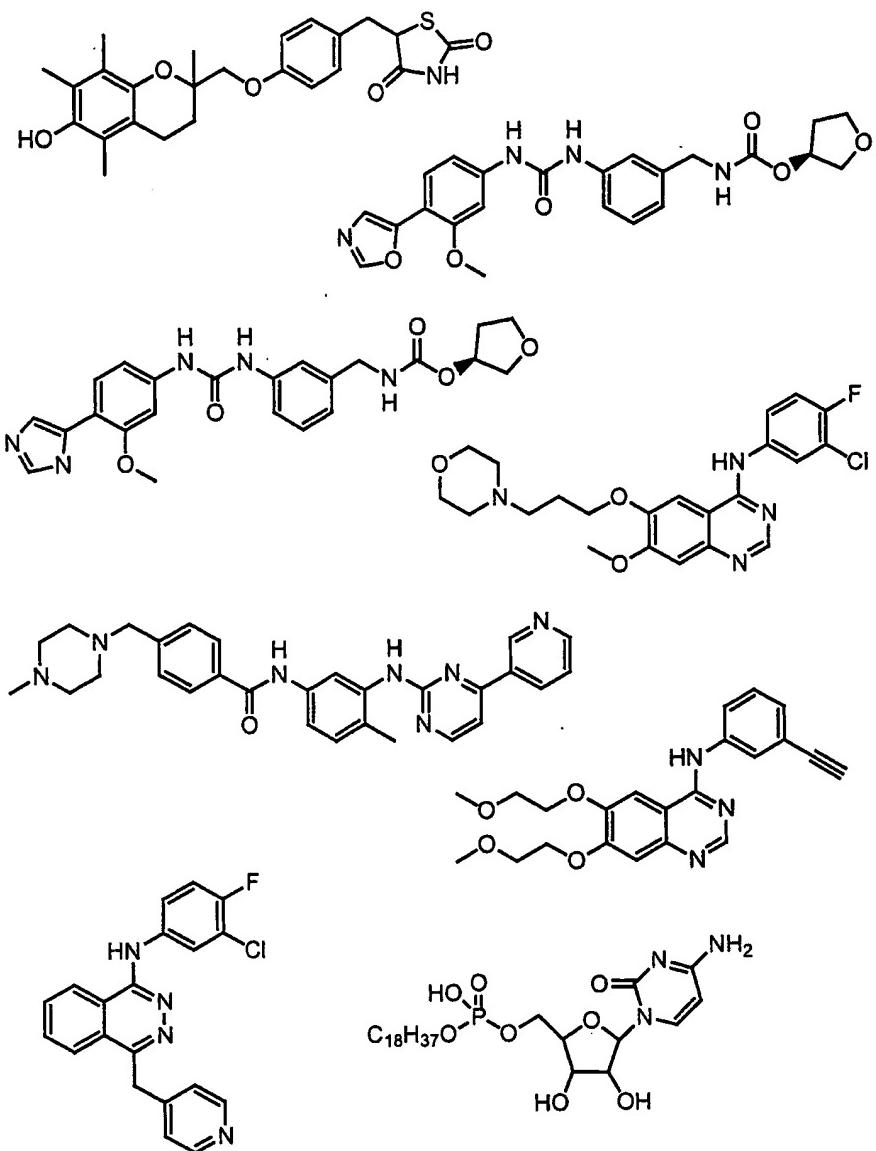
25 M1a, M1c, and M1d are independently 0 or 1;

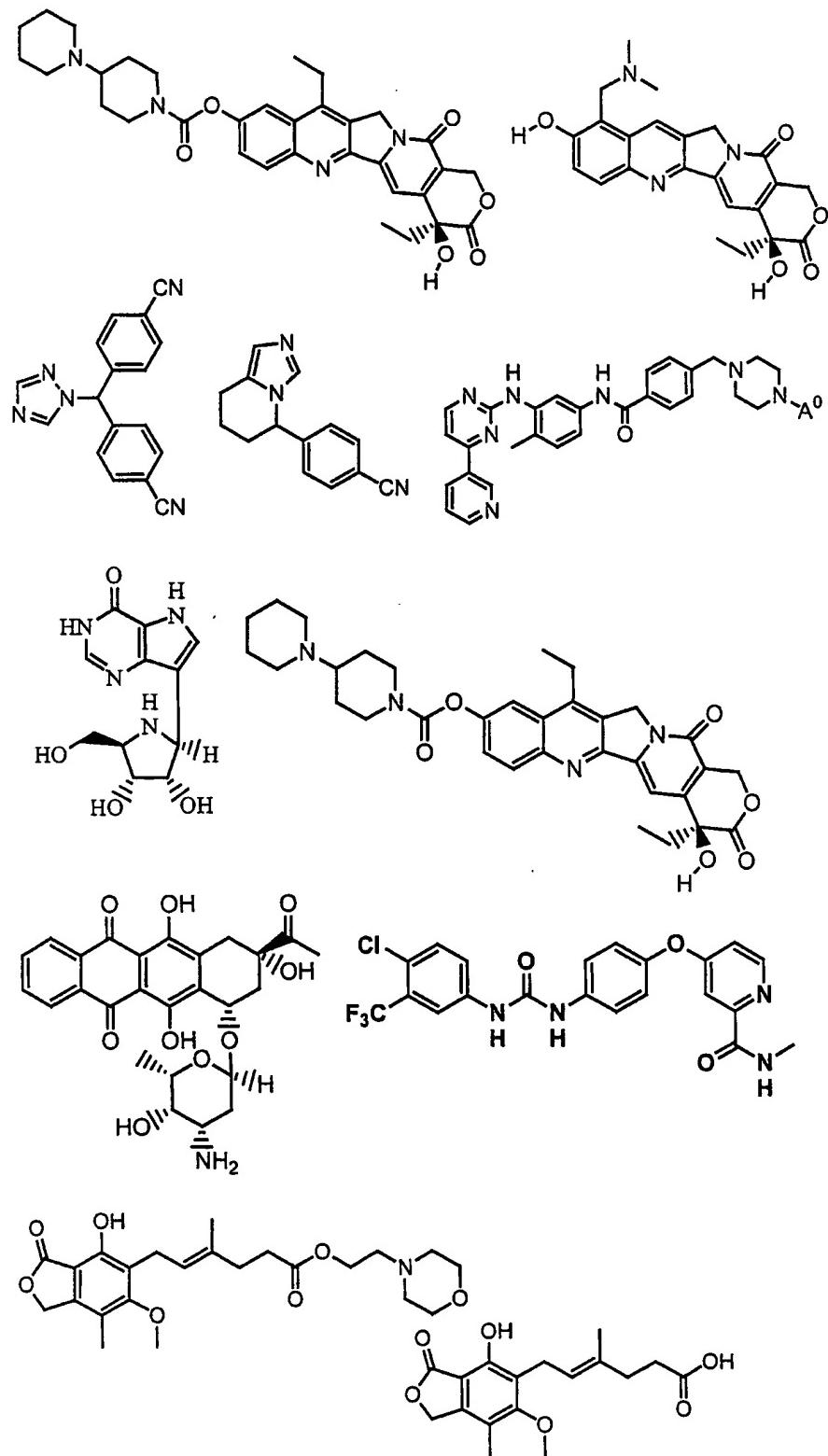
 M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

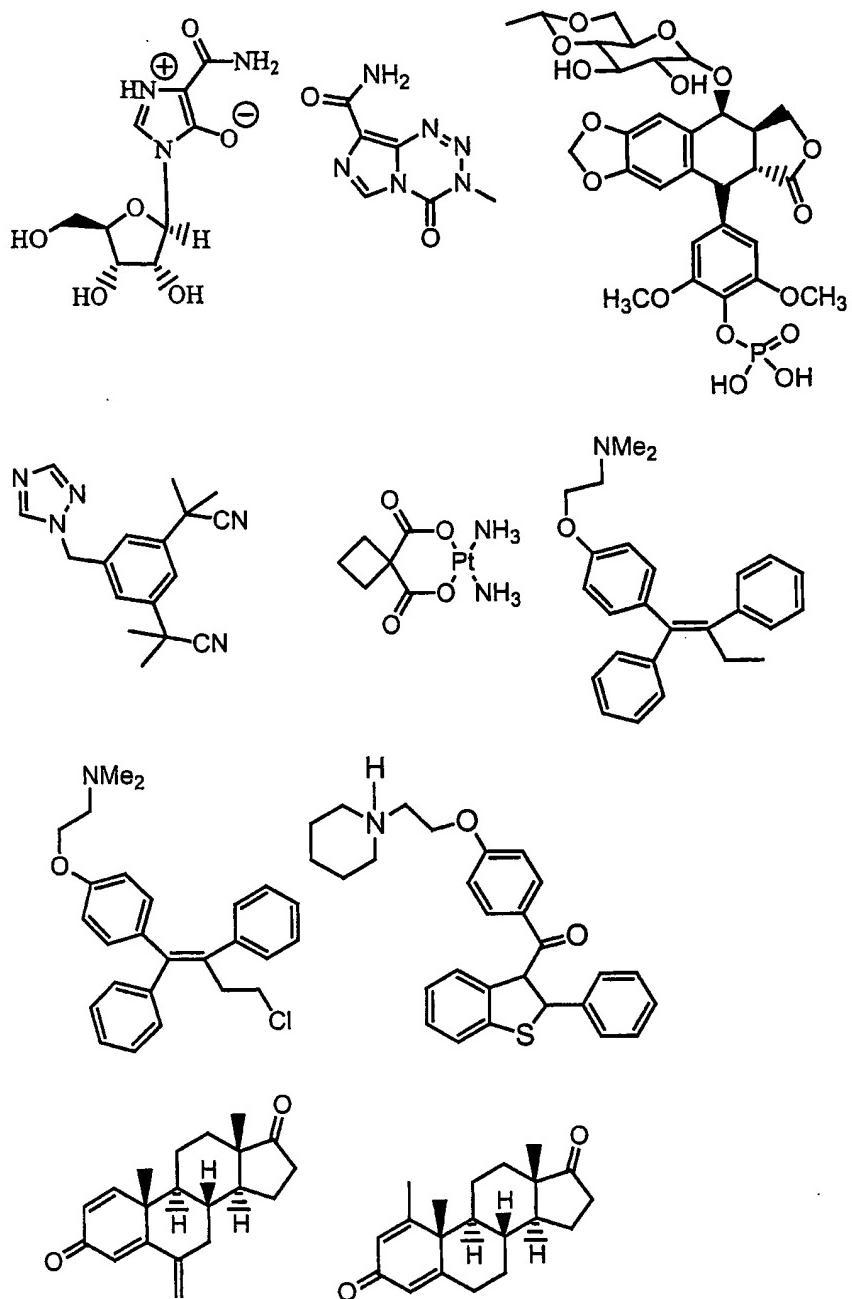
In another embodiment the invention provides a conjugate, or a

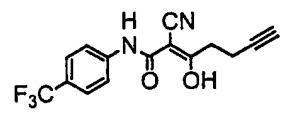
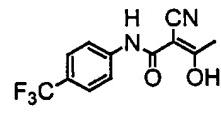
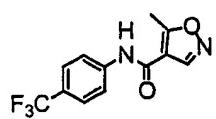
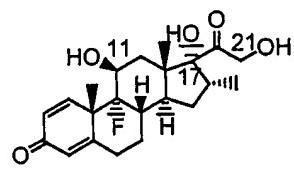
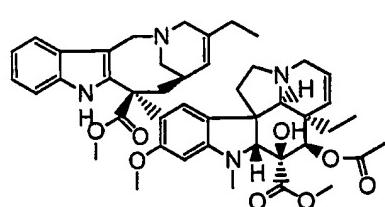
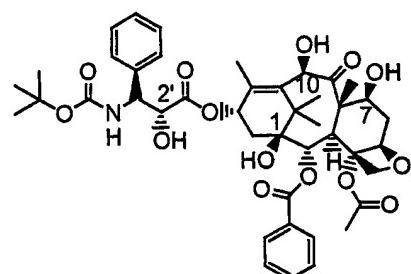
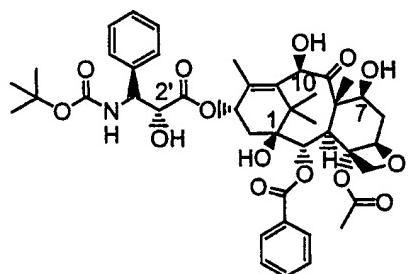
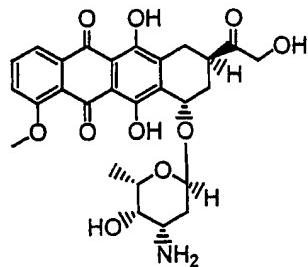
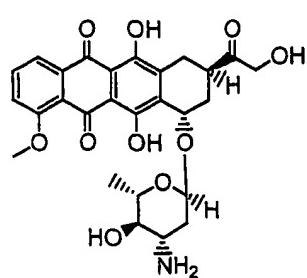
pharmaceutically acceptable salt or solvate thereof, that is a compound of any

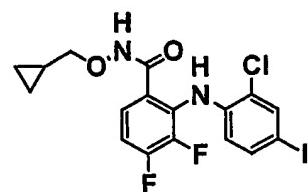
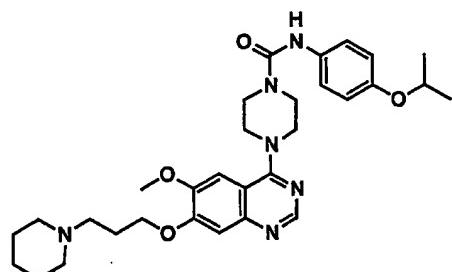
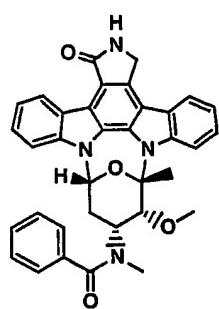
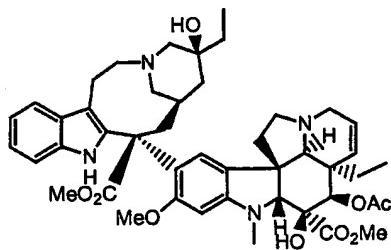
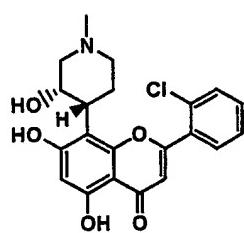
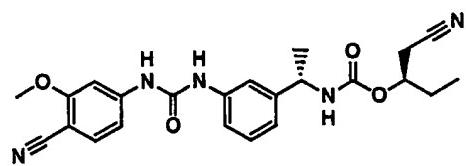
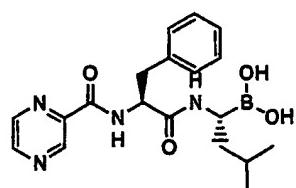
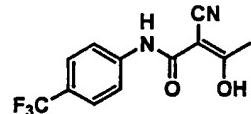
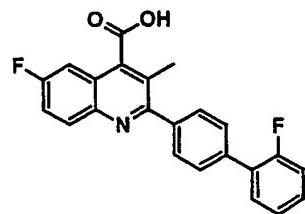
30 one of the following formulae:

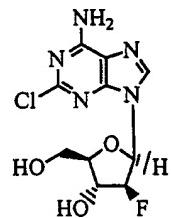
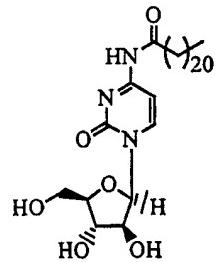
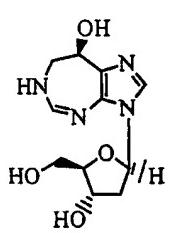
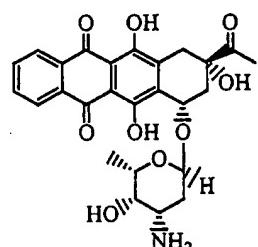
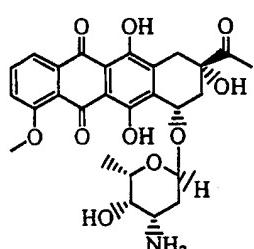
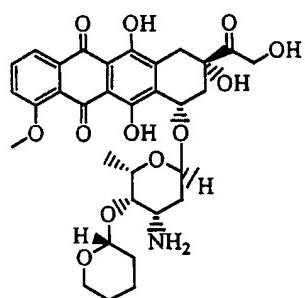
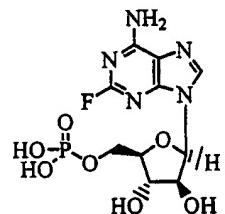
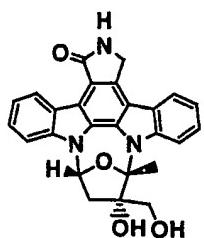
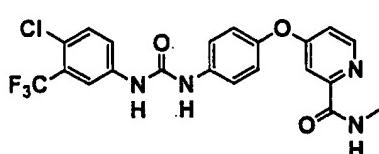
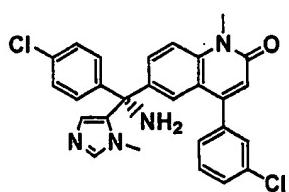


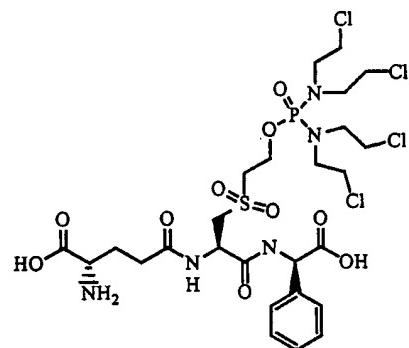
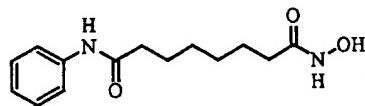
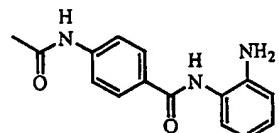
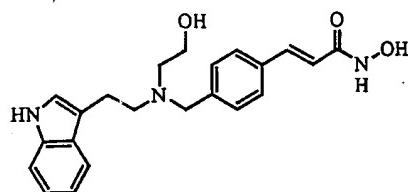
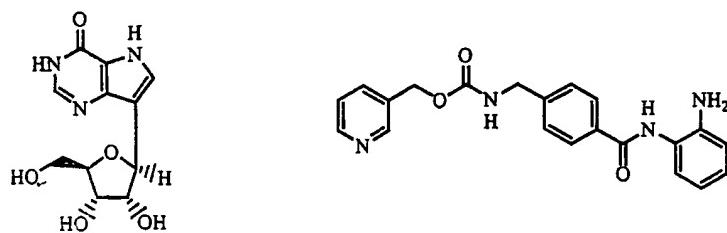


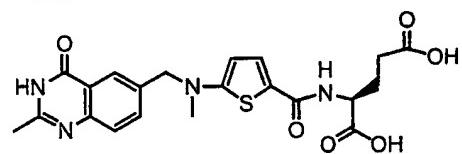
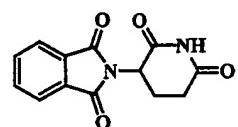
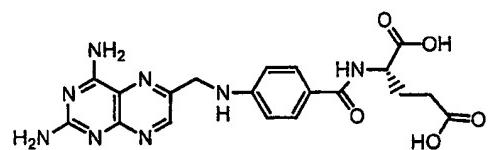
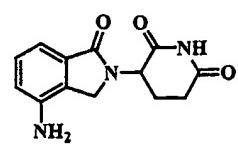
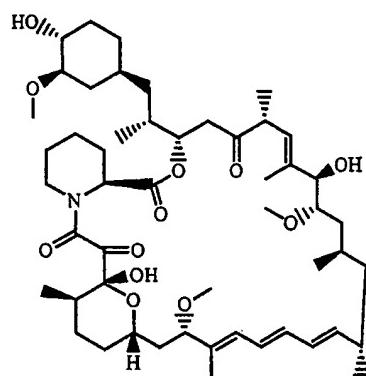
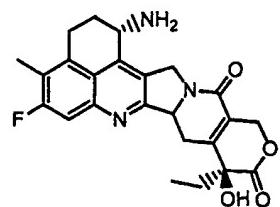
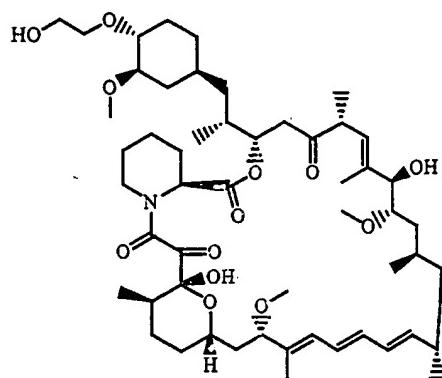


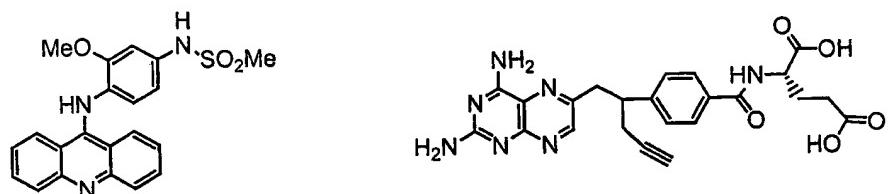
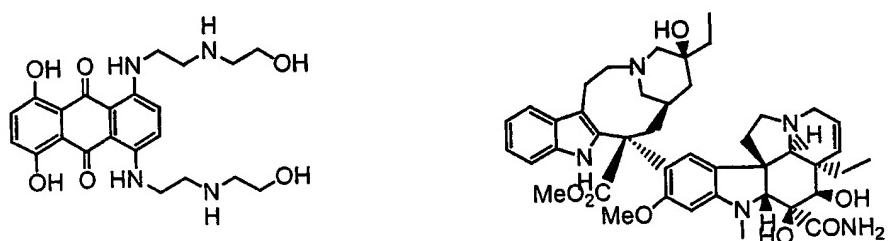
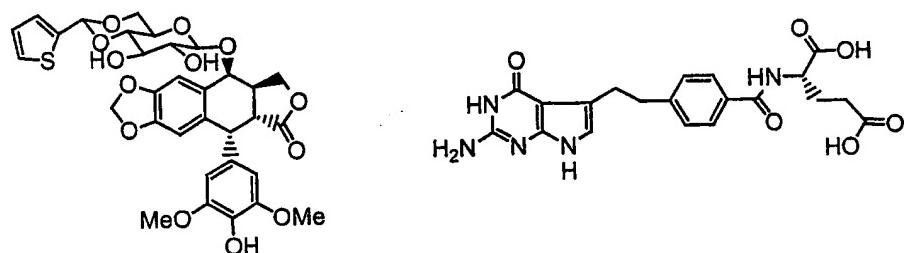
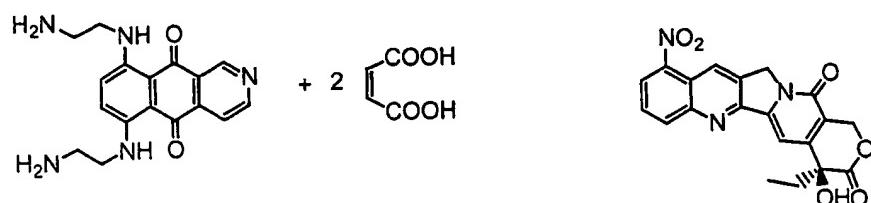


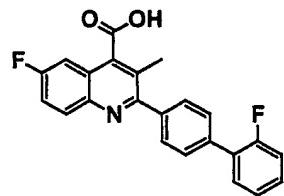
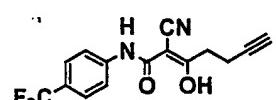
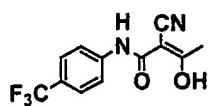
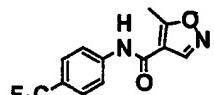
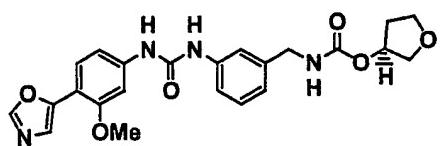
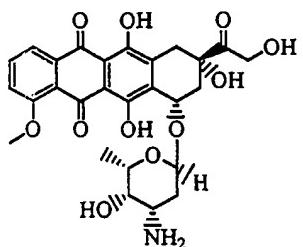
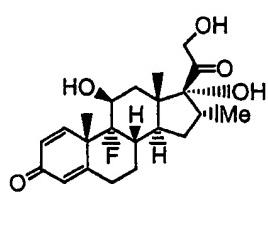
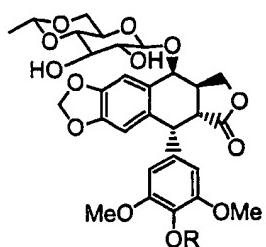
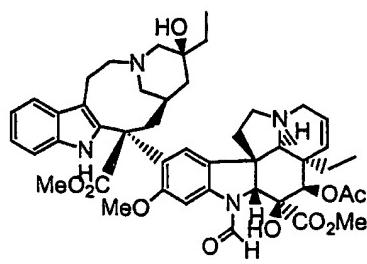


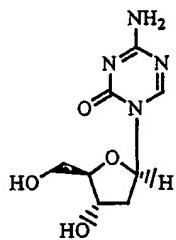
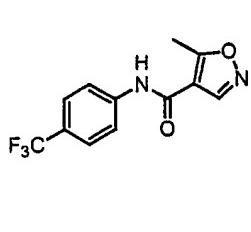
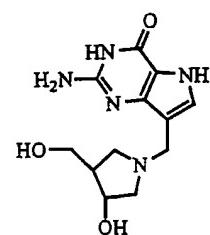
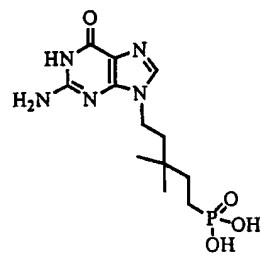
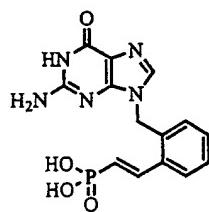
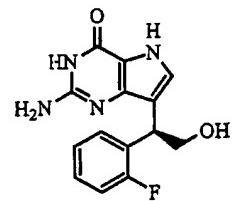
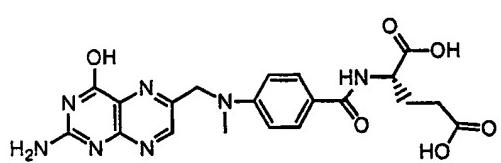
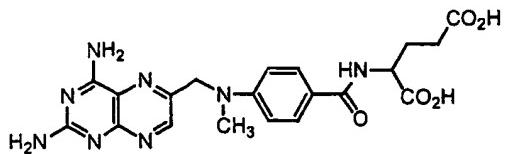


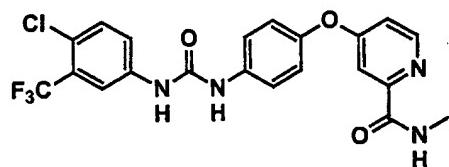
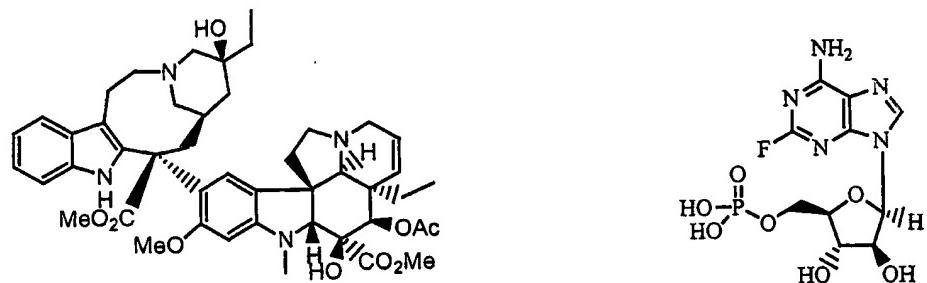
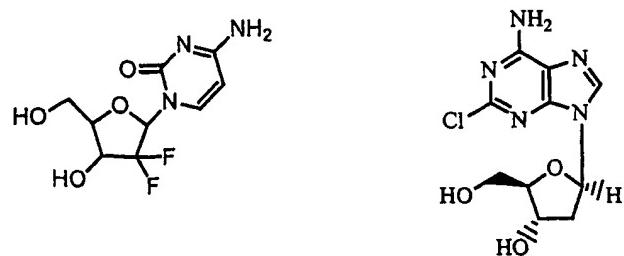








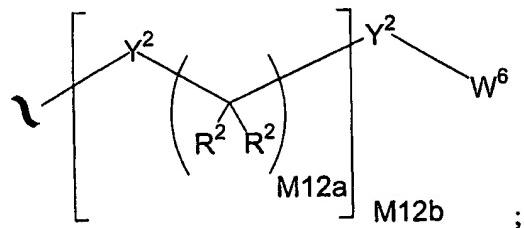




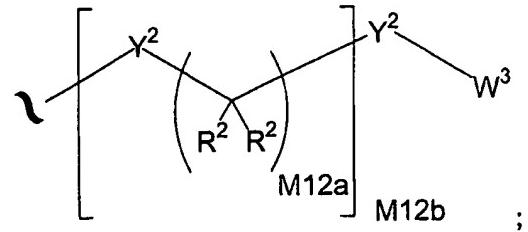
that is substituted with one or more groups A^0 , wherein:

A^0 is A^1 , A^2 or W^3 with the proviso that the conjugate includes at least one A^1 ;

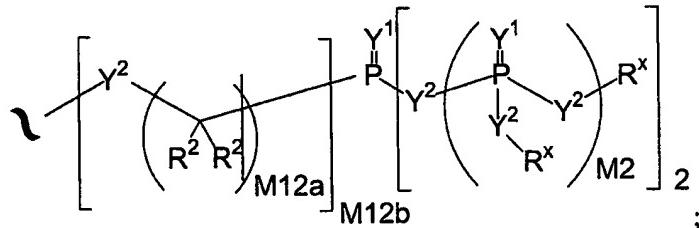
5 A^1 is:



A^2 is:



A³ is:

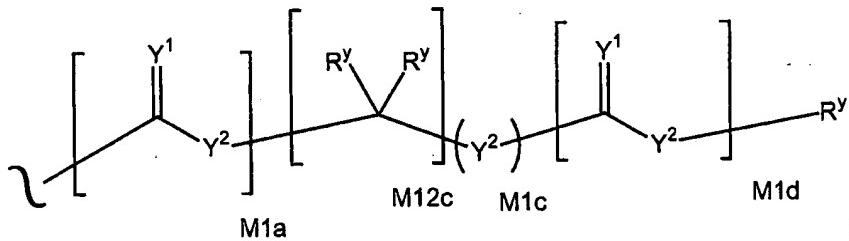


Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or

5 N(N(R^x)(R^x));

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x),
N(N(R^x)(R^x)), -S(O)_{M2}- or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two
phosphorous atoms Y² can also be C(R²)(R²);

R^x is independently H, R¹, R², W³, a protecting group, or the formula:



10

wherein:

R^y is independently H, W³, R² or a protecting group;

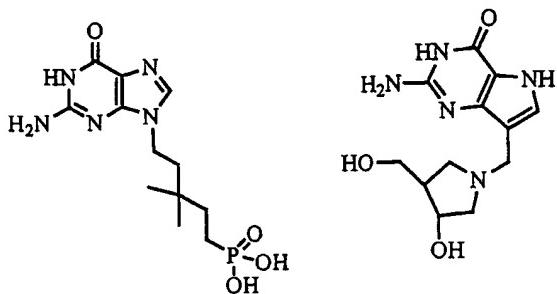
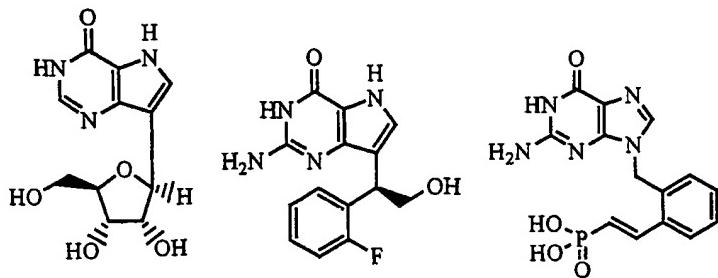
R¹ is independently H or alkyl of 1 to 18 carbon atoms;

15 R² is independently H, R¹, R³ or R⁴ wherein each R⁴ is independently
substituted with 0 to 3 R³ groups or taken together at a carbon atom, two R²
groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3
R³ groups;

R³ is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R³ is bound to a
heteroatom, then R³ is R^{3c} or R^{3d};

20 R^{3a} is F, Cl, Br, I, -CN, N₃ or -NO₂;

- R^{3b} is Y¹;
- R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)₂R^x, -S(O)(OR^x), -S(O)₂(OR^x), -OC(Y¹)R^x, -OC(Y¹)OR^x, -OC(Y¹)(N(R^x)(R^x)), -SC(Y¹)R^x, -SC(Y¹)OR^x, -SC(Y¹)(N(R^x)(R^x)), -N(R^x)C(Y¹)R^x, -N(R^x)C(Y¹)OR^x, or -N(R^x)C(Y¹)(N(R^x)(R^x));
- 5 R^{3d} is -C(Y¹)R^x, -C(Y¹)OR^x or -C(Y¹)(N(R^x)(R^x));
- R⁴ is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;
- R⁵ is R⁴ wherein each R⁴ is substituted with 0 to 3 R³ groups;
- 10 W³ is W⁴ or W⁵;
- W⁴ is R⁵, -C(Y¹)R⁵, -C(Y¹)W⁵, -SO_{M2}R⁵, or -SO_{M2}W⁵;
- W⁵ is carbocycle or heterocycle wherein W⁵ is independently substituted with 0 to 3 R² groups;
- 15 W⁶ is W³ independently substituted with 1, 2, or 3 A³ groups;
- M2 is 0, 1 or 2;
- M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M1a, M1c, and M1d are independently 0 or 1;
- M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.
- 20 In another embodiment the invention provides a conjugate, or a pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of the following formulae:

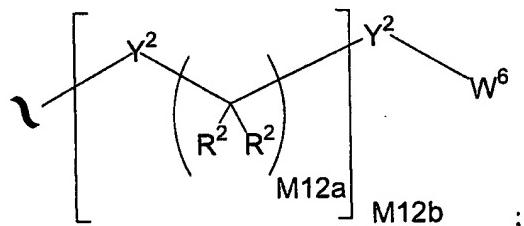


that is substituted with one or more groups A⁰, wherein:

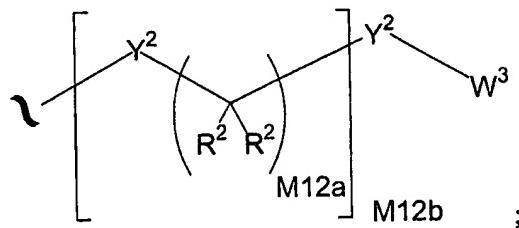
A⁰ is A¹, A² or W³ with the proviso that the conjugate includes at least

5 one A¹;

A¹ is:

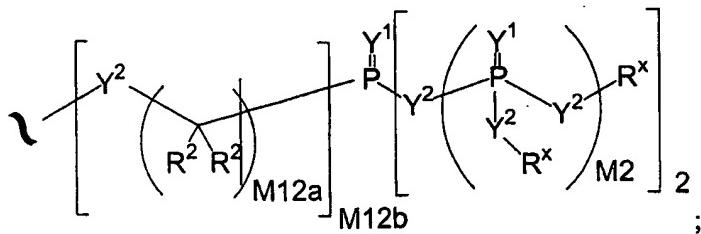


A² is:



10

A³ is:



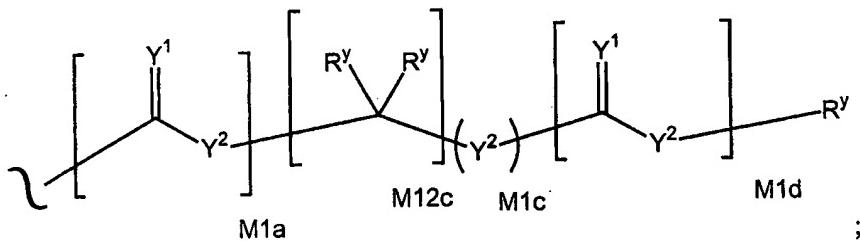
Y^1 is independently O, S, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x), or

N(N(R^x))(R x));

Y^2 is independently a bond, O, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x),

- 5 N(N(R^x))(R x)), -S(O) M_2- , or -S(O) M_2- S(O) M_2- ; and when Y^2 joins two phosphorous atoms Y^2 can also be C(R^2)(R^2);

R^x is independently H, R 1 , R 2 , W 3 , a protecting group, or the formula:



wherein:

- 10 Ry is independently H, W 3 , R 2 or a protecting group;

R 1 is independently H or alkyl of 1 to 18 carbon atoms;

R 2 is independently H, R 1 , R 3 or R 4 wherein each R 4 is independently substituted with 0 to 3 R 3 groups or taken together at a carbon atom, two R 2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3

- 15 R 3 groups;

R 3 is R 3a , R 3b , R 3c or R 3d , provided that when R 3 is bound to a heteroatom, then R 3 is R 3c or R 3d ;

R 3a is F, Cl, Br, I, -CN, N₃ or -NO₂;

R 3b is Y 1 ;

- 20 R 3c is -R x , -N(R^x)(R^x), -SR x , -S(O)R x , -S(O)₂R x , -S(O)(OR x), -S(O)₂(OR x), -OC(Y 1)R x , -OC(Y 1)OR x , -OC(Y 1)(N(R^x)(R^x)), -SC(Y 1)R x , -SC(Y 1)OR x , -SC(Y 1)(N(R^x)(R^x)), -N(R^x)C(Y 1)R x , -N(R^x)C(Y 1)OR x , or -N(R^x)C(Y 1)(N(R^x)(R^x));

R 3d is -C(Y 1)R x , -C(Y 1)OR x or -C(Y 1)(N(R^x)(R^x));

R⁴ is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R⁵ is R⁴ wherein each R⁴ is substituted with 0 to 3 R³ groups;

W³ is W⁴ or W⁵;

5 W⁴ is R⁵, -C(Y¹)R⁵, -C(Y¹)W⁵, -SO_{M2}R⁵, or -SO_{M2}W⁵;

W⁵ is carbocycle or heterocycle wherein W⁵ is independently substituted with 0 to 3 R² groups;

W⁶ is W³ independently substituted with 1, 2, or 3 A³ groups;

M2 is 0, 1 or 2;

10 M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

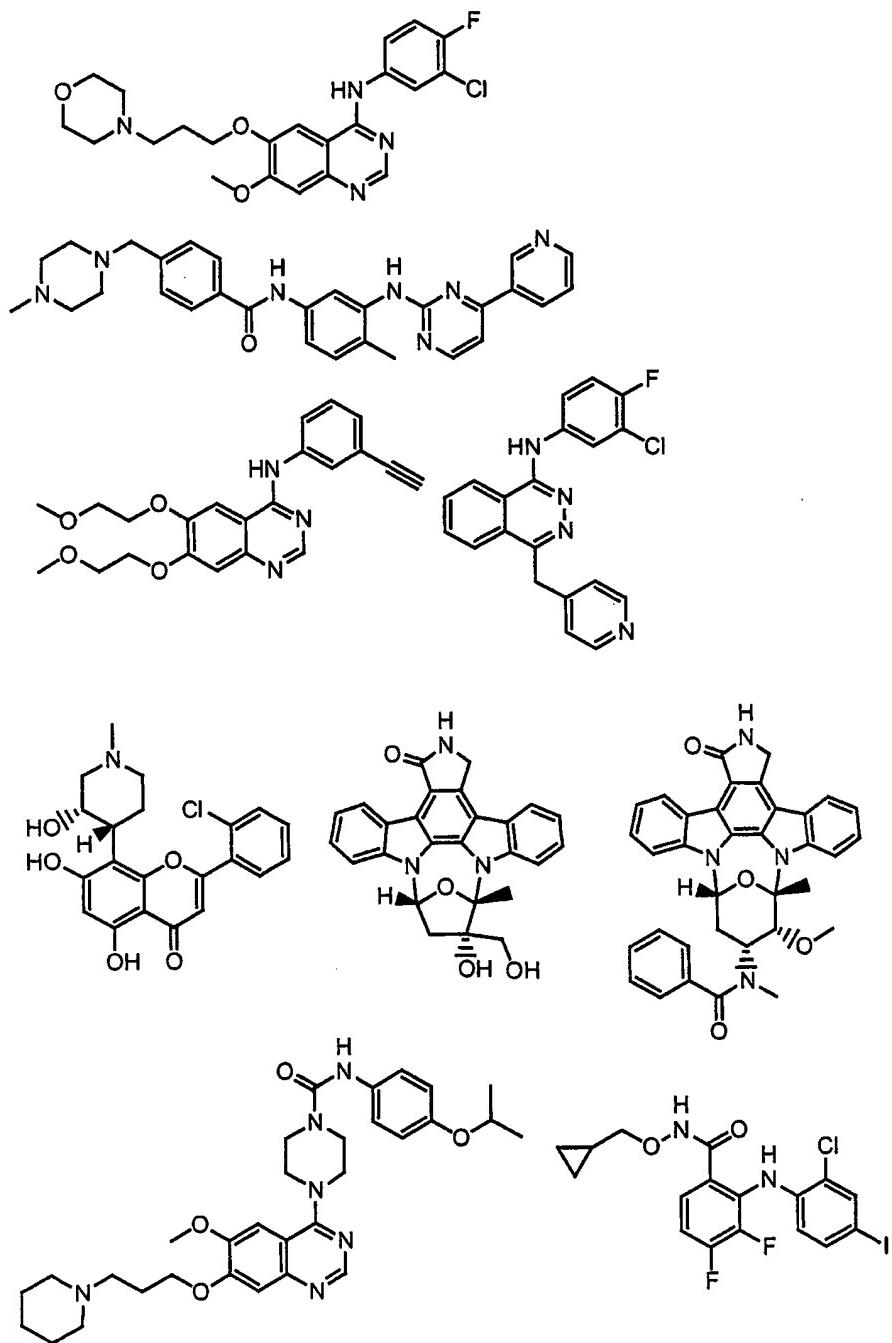
M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

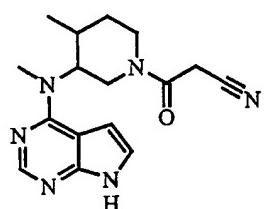
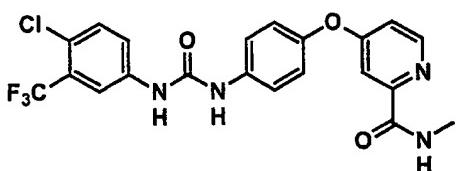
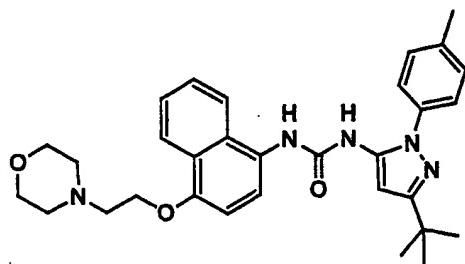
M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another embodiment the invention provides a conjugate, or a

15 pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of the following formulae:



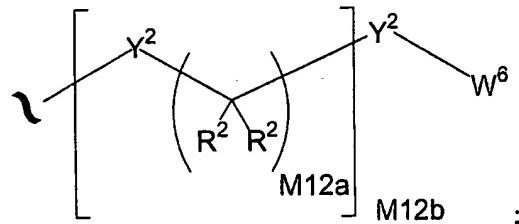


that is substituted with one or more groups A^0 , wherein:

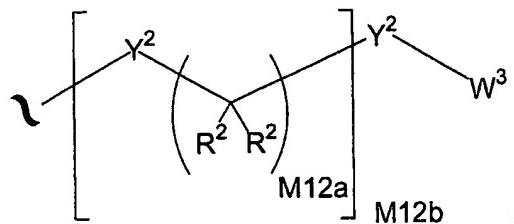
A^0 is A^1 , A^2 or W^3 with the proviso that the conjugate includes at least

5 one A^1 ;

A^1 is:

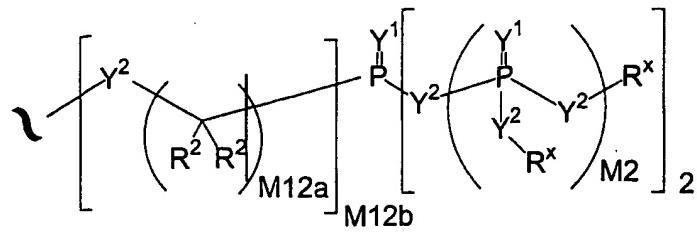


A^2 is:



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A^3 is:

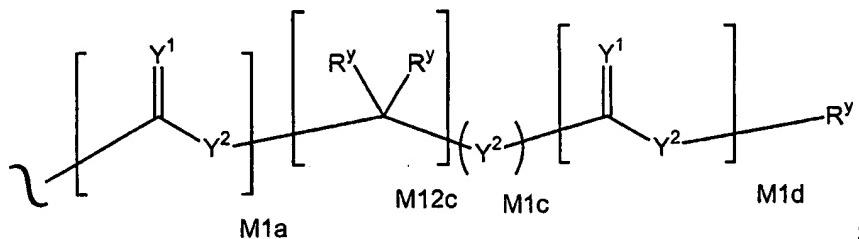


Y^1 is independently O, S, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x), or N(N(R^x))(R x);

Y^2 is independently a bond, O, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x),

- 5 N(N(R^x))(R x)), -S(O) $_{M2}$ - or -S(O) $_{M2}$ -S(O) $_{M2}$ -; and when Y^2 joins two phosphorous atoms Y^2 can also be C(R^2)(R 2);

R^x is independently H, R 1 , R 2 , W 3 , a protecting group, or the formula:



wherein:

- 10 R^y is independently H, W 3 , R 2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

- R^2 is independently H, R 1 , R 3 or R 4 wherein each R 4 is independently substituted with 0 to 3 R 3 groups or taken together at a carbon atom, two R 2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R 3 groups;

R^3 is R 3a , R 3b , R 3c or R 3d , provided that when R 3 is bound to a heteroatom, then R 3 is R 3c or R 3d ;

R 3a is F, Cl, Br, I, -CN, N₃ or -NO₂;

R 3b is Y 1 ;

- 20 R 3c is -R x , -N(R^x)(R^x), -SR x , -S(O)R x , -S(O)₂R x , -S(O)(OR x), -S(O)₂(OR x), -OC(Y 1)R x , -OC(Y 1)OR x , -OC(Y 1)(N(R^x)(R^x)), -SC(Y 1)R x , -SC(Y 1)OR x , -SC(Y 1)(N(R^x)(R^x)), -N(R^x)C(Y 1)R x , -N(R^x)C(Y 1)OR x , or -N(R^x)C(Y 1)(N(R^x)(R^x));

R 3d is -C(Y 1)R x , -C(Y 1)OR x or -C(Y 1)(N(R^x)(R^x));

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5 ;

5 W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

$M2$ is 0, 1 or 2;

10 $M12a$ is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

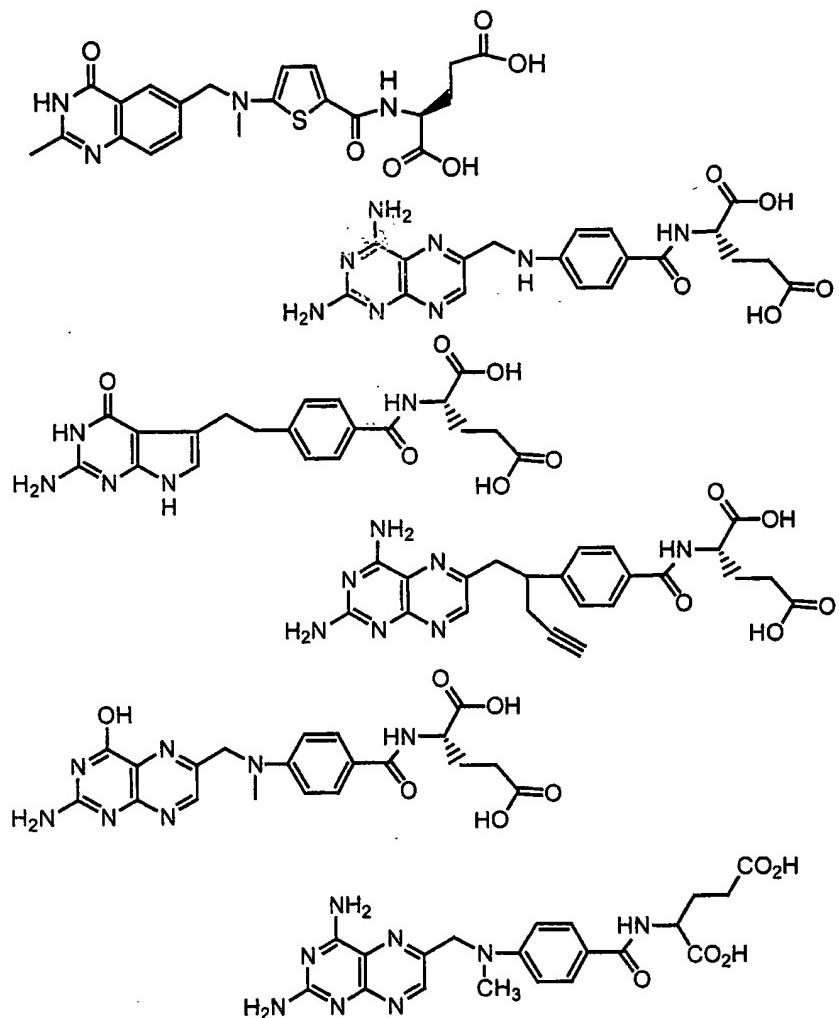
$M12b$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

$M1a$, $M1c$, and $M1d$ are independently 0 or 1;

$M12c$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another embodiment the invention provides a conjugate, or a

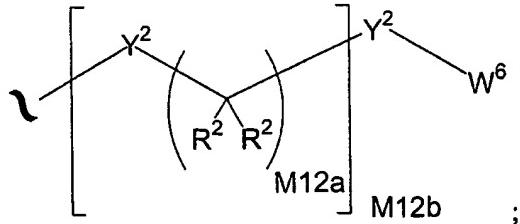
15 pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of the following formulae:



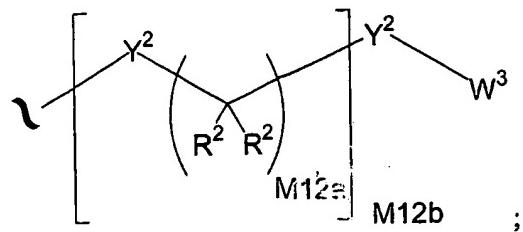
that is substituted with one or more groups A^0 , wherein:

A^0 is A^1 , A^2 or W^3 with the proviso that the conjugate includes at least
5 one A^1 ;

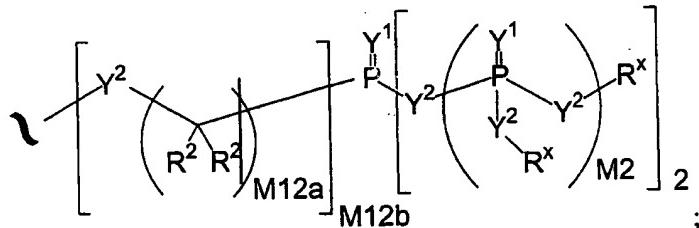
A^1 is:



A² is:



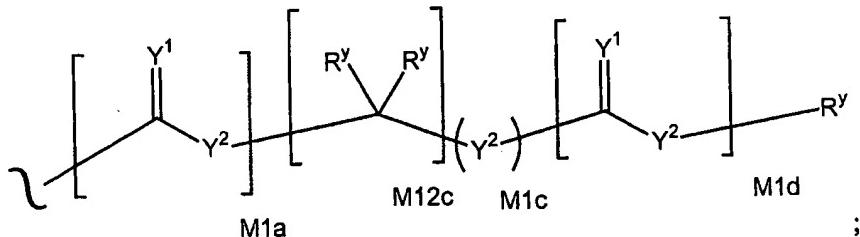
A³ is:



5 Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or
N(N(R^x)(R^x));

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x),
N(N(R^x)(R^x)), -S(O)_{M2}- , or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two
phosphorous atoms Y² can also be C(R²)(R²);

10 R^x is independently H, R¹, R², W³, a protecting group, or the formula:



wherein:

R^y is independently H, W³, R² or a protecting group;

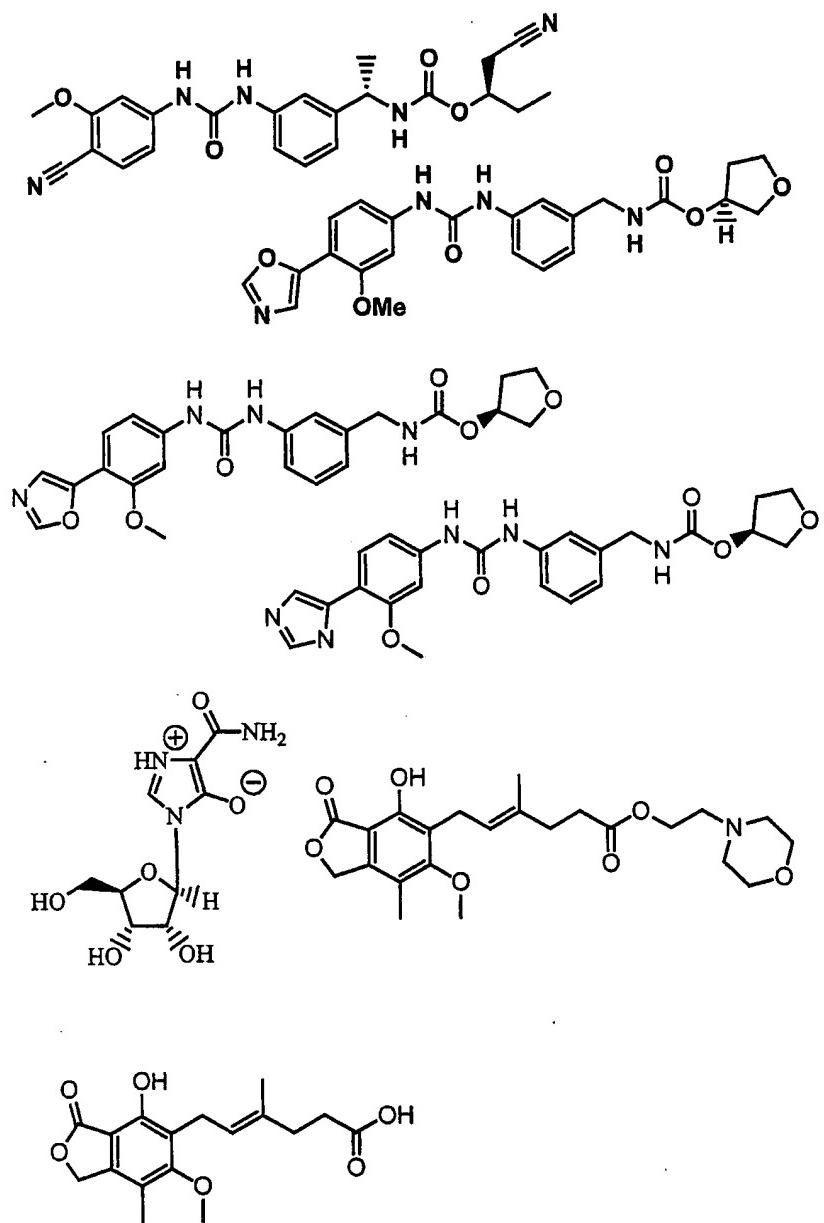
R¹ is independently H or alkyl of 1 to 18 carbon atoms;

15 R² is independently H, R¹, R³ or R⁴ wherein each R⁴ is independently
substituted with 0 to 3 R³ groups or taken together at a carbon atom, two R²
groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3
R³ groups;

R³ is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R³ is bound to a

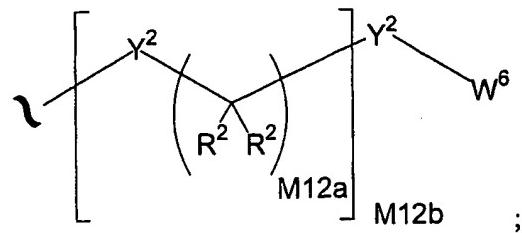
20 heteroatom, then R³ is R^{3c} or R^{3d};

- R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;
- R^{3b} is Y^1 ;
- R^{3c} is $-R^X$, $-N(R^X)(R^X)$, $-SR^X$, $-S(O)R^X$, $-S(O)_2R^X$, $-S(O)(OR^X)$, $-S(O)_2(OR^X)$, $-OC(Y^1)R^X$, $-OC(Y^1)OR^X$, $-OC(Y^1)(N(R^X)(R^X))$, $-SC(Y^1)R^X$, $-SC(Y^1)OR^X$, $-SC(Y^1)(N(R^X)(R^X))$, $-N(R^X)C(Y^1)R^X$, $-N(R^X)C(Y^1)OR^X$, or $-N(R^X)C(Y^1)(N(R^X)(R^X))$;
- 5 R^{3d} is $-C(Y^1)R^X$, $-C(Y^1)OR^X$ or $-C(Y^1)(N(R^X)(R^X))$;
- R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;
- 10 R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;
- W^3 is W^4 or W^5 ;
- W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;
- W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;
- 15 W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;
- $M2$ is 0, 1 or 2;
- $M12a$ is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- $M12b$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- $M1a$, $M1c$, and $M1d$ are independently 0 or 1;
- 20 $M12c$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.
- In another embodiment the invention provides a conjugate, or a pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of the following formulae:

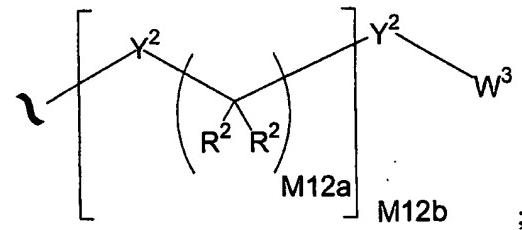


that is substituted with one or more groups A^0 , wherein:

- A^0 is A^1 , A^2 or W^3 with the proviso that the conjugate includes at least
 5 one A^1 ;
 A^1 is:

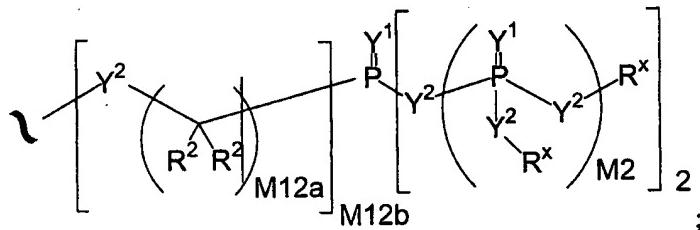


A² is:



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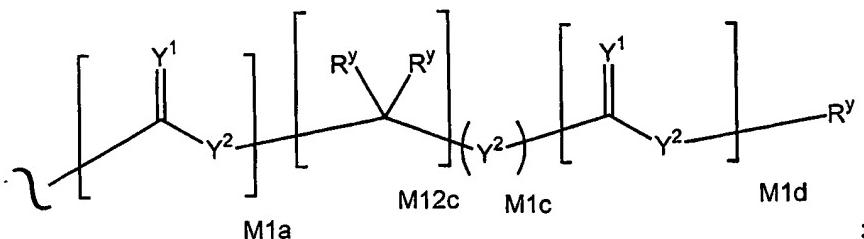
A³ is:



Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

- Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x),
10 N(N(R^x)(R^x)), -S(O)_{M2}- , or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two
phosphorous atoms Y² can also be C(R²)(R²);

R^x is independently H, R¹, R², W³, a protecting group, or the formula:



wherein:

- 15 R^y is independently H, W³, R² or a protecting group;

R¹ is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1 , R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

5 R^3 is R^{3a} , R^{3b} , R^{3c} or R^{3d} , provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d} ;

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1 ;

R^{3c} is $-R^X$, $-N(R^X)(R^X)$, $-SR^X$, $-S(O)R^X$, $-S(O)_2R^X$, $-S(O)(OR^X)$, $-$

10 $S(O)_2(OR^X)$, $-OC(Y^1)R^X$, $-OC(Y^1)OR^X$, $-OC(Y^1)(N(R^X)(R^X))$, $-SC(Y^1)R^X$, $-$
 $SC(Y^1)OR^X$, $-SC(Y^1)(N(R^X)(R^X))$, $-N(R^X)C(Y^1)R^X$, $-N(R^X)C(Y^1)OR^X$, or $-$
 $N(R^X)C(Y^1)(N(R^X)(R^X))$;

R^{3d} is $-C(Y^1)R^X$, $-C(Y^1)OR^X$ or $-C(Y^1)(N(R^X)(R^X))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms,

15 or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5 ;

W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted

20 with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

$M2$ is 0, 1 or 2;

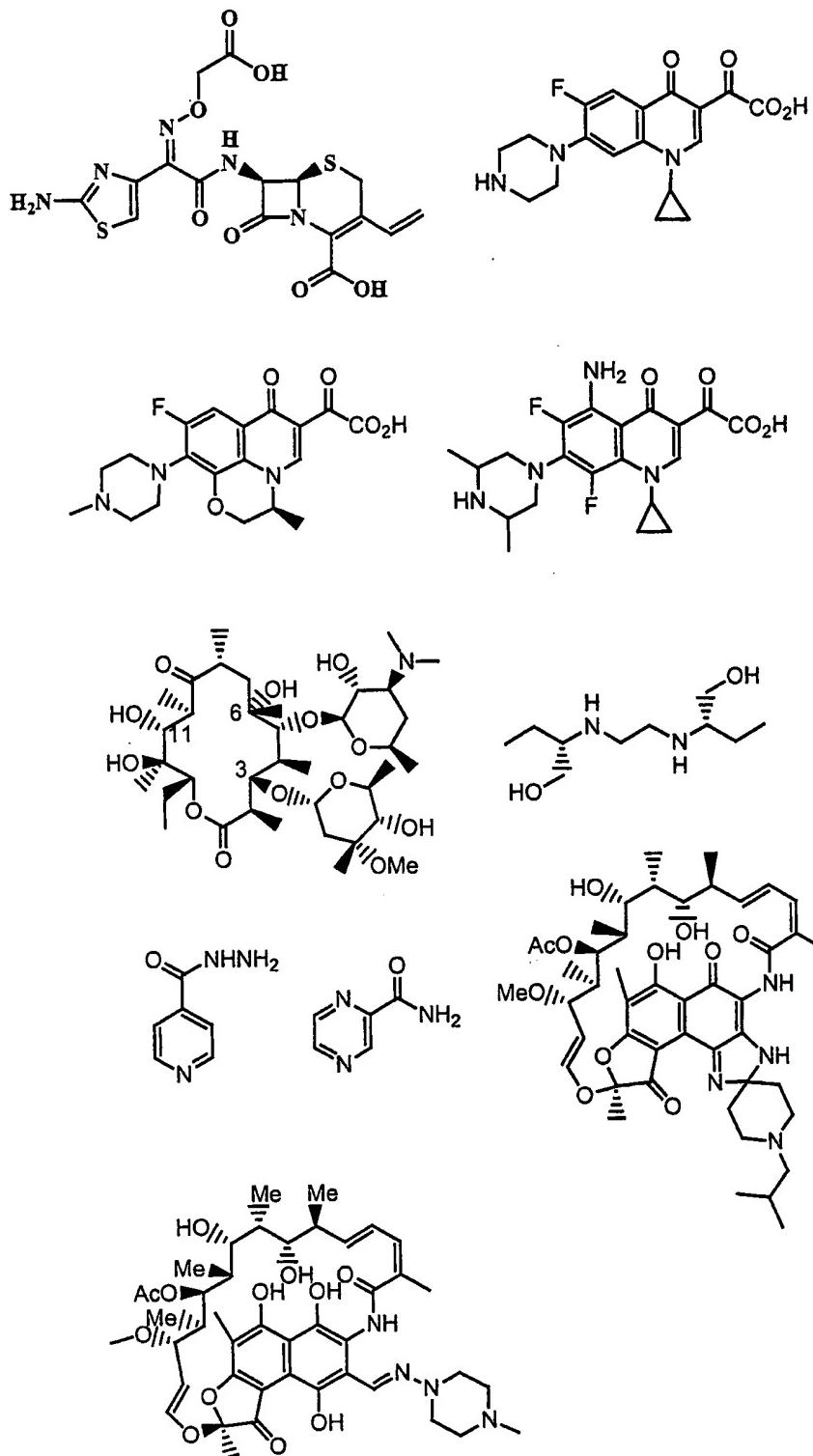
$M12a$ is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

$M12b$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

25 $M1a$, $M1c$, and $M1d$ are independently 0 or 1;

$M12c$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another embodiment the invention provides a conjugate, or a pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of the following formulae:

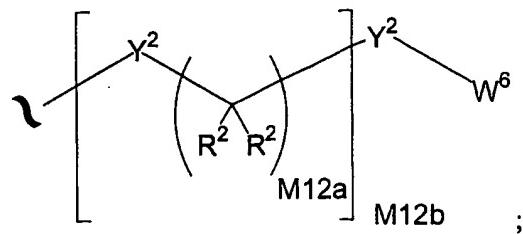


that is substituted with one or more groups A⁰, wherein:

A⁰ is A¹, A² or W³ with the proviso that the conjugate includes at least one A¹;

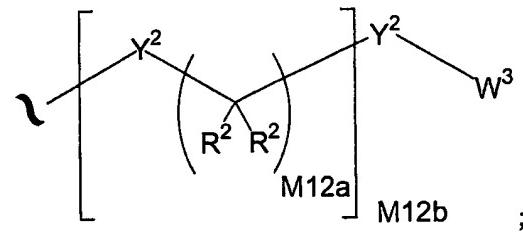
A¹ is:

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;

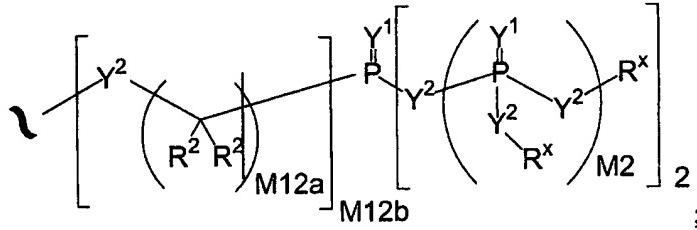
A² is:



;

A³ is:

10



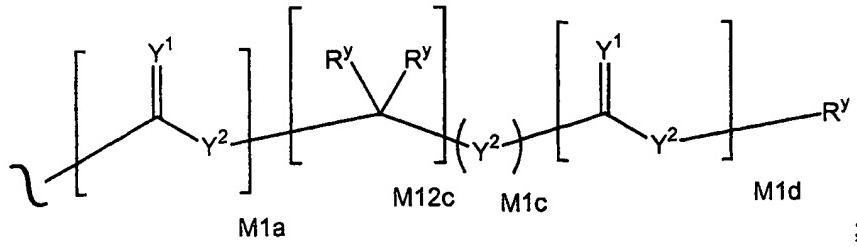
;

Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)), -S(O)_{M2}- , or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two phosphorous atoms Y² can also be C(R²)(R²);

15

R^x is independently H, R¹, R², W³, a protecting group, or the formula:



wherein:

R^y is independently H, W^3 , R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

5 R^2 is independently H, R^1 , R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a} , R^{3b} , R^{3c} or R^{3d} , provided that when R^3 is bound to a

10 heteroatom, then R^3 is R^{3c} or R^{3d} ;

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1 ;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-$

15 $SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

20 R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5 ;

W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

25 W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

$M2$ is 0, 1 or 2;

$M12a$ is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

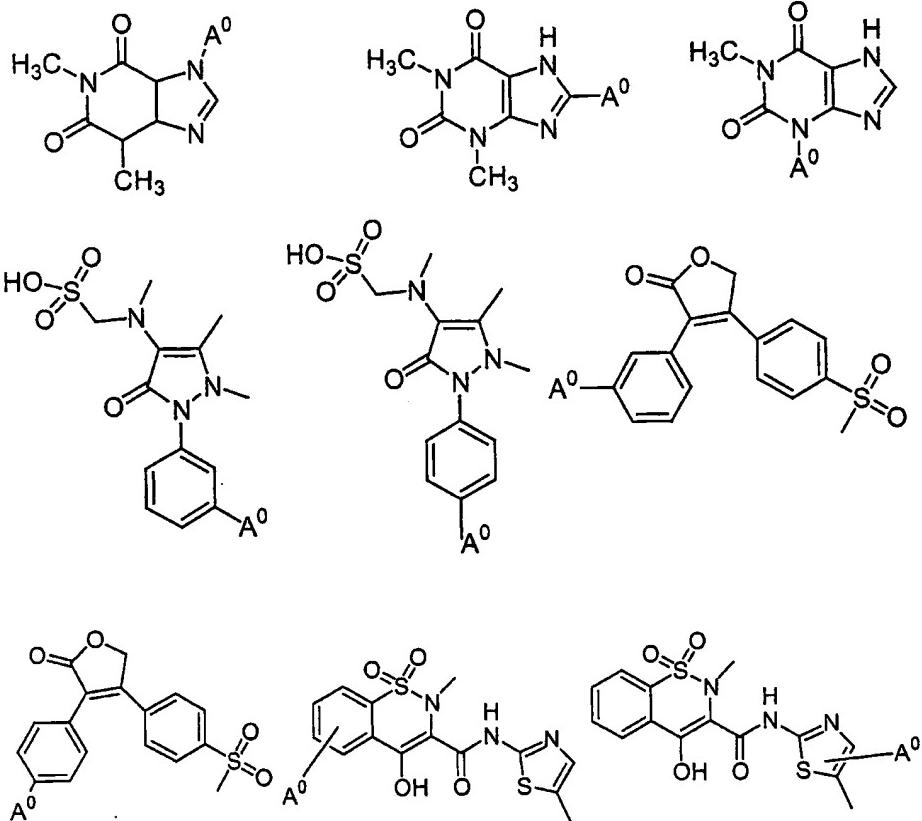
$M12b$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

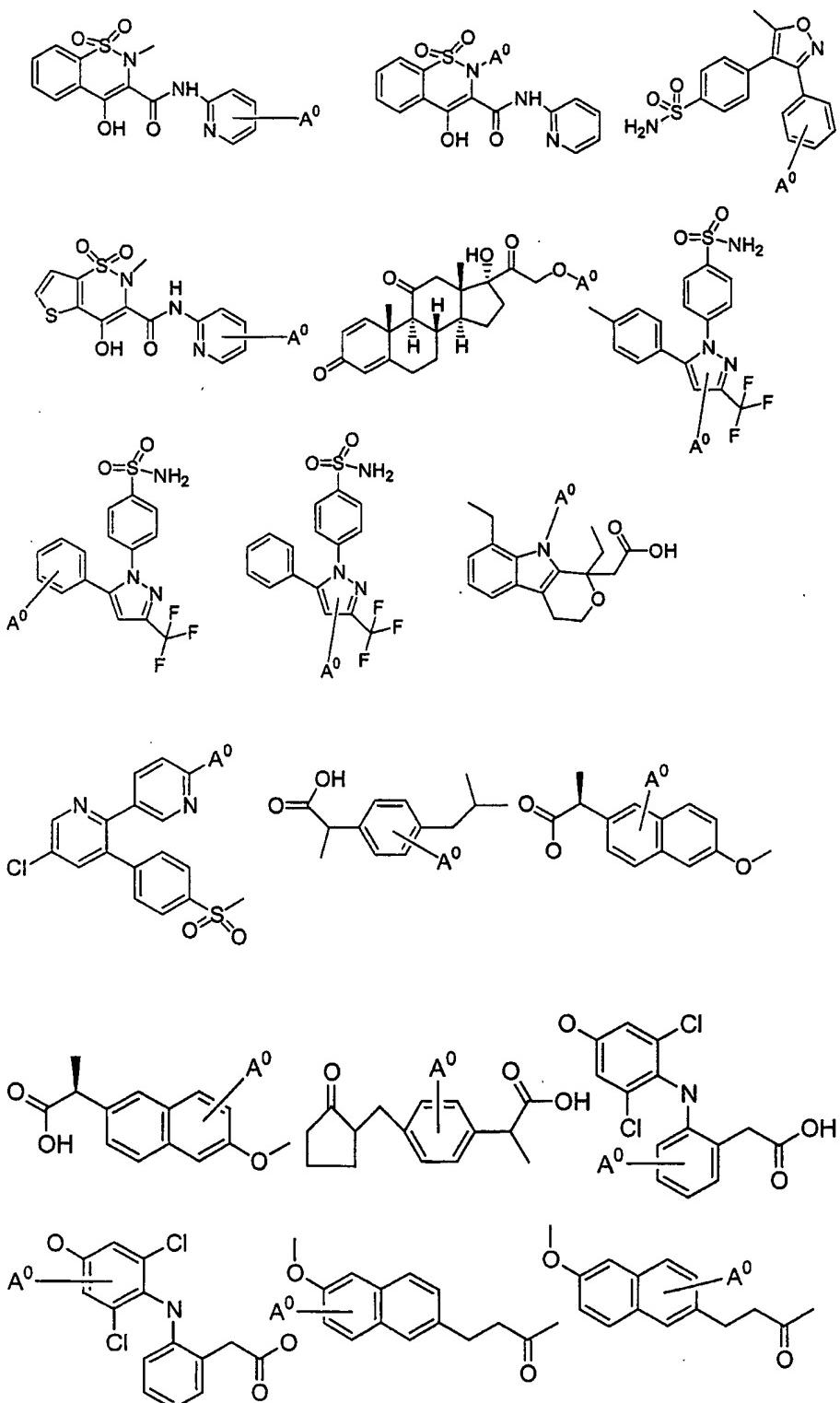
M1a, M1c, and M1d are independently 0 or 1;

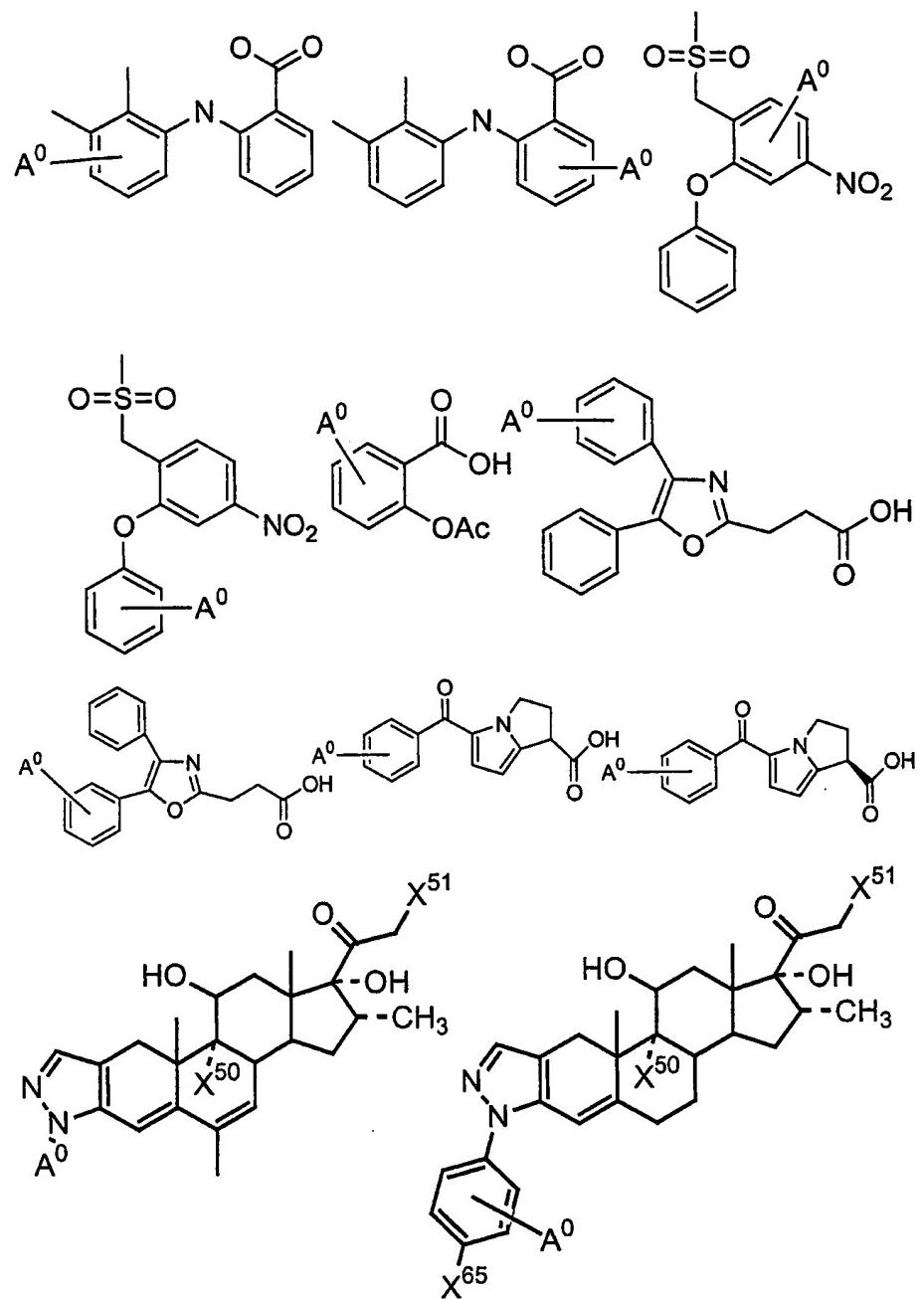
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

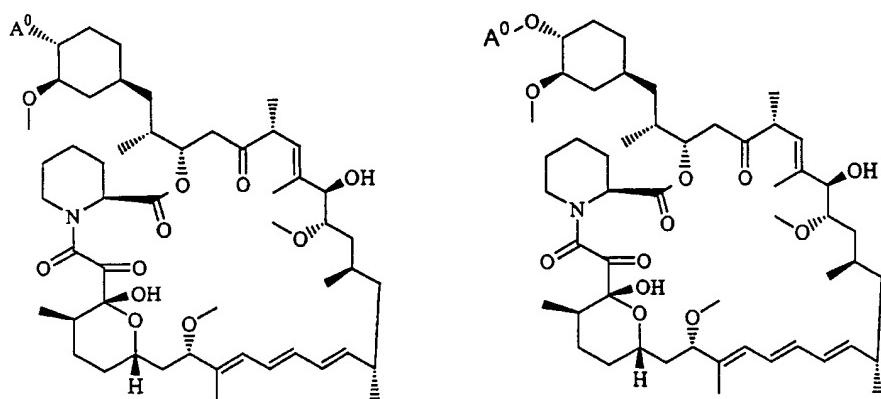
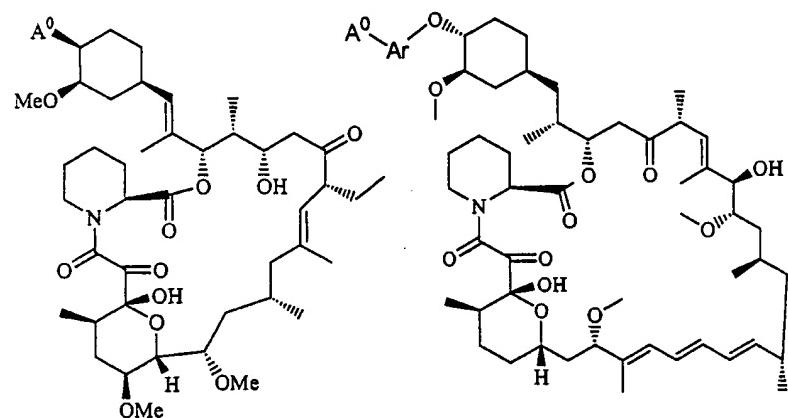
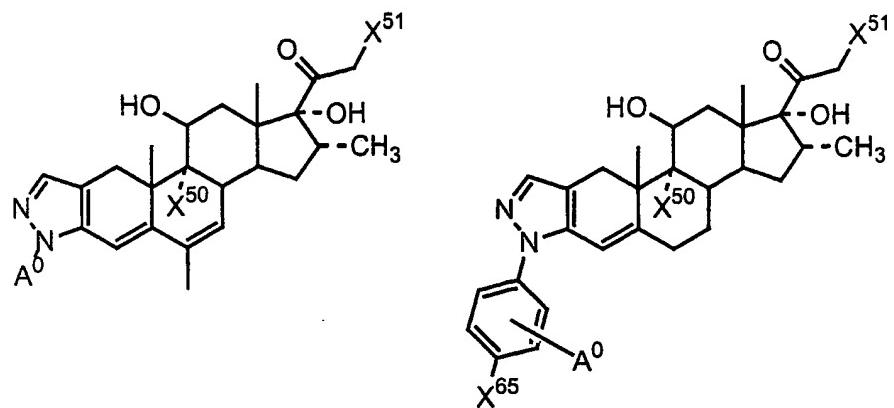
In another embodiment the invention provides a conjugate, which has any one of the following formulae:

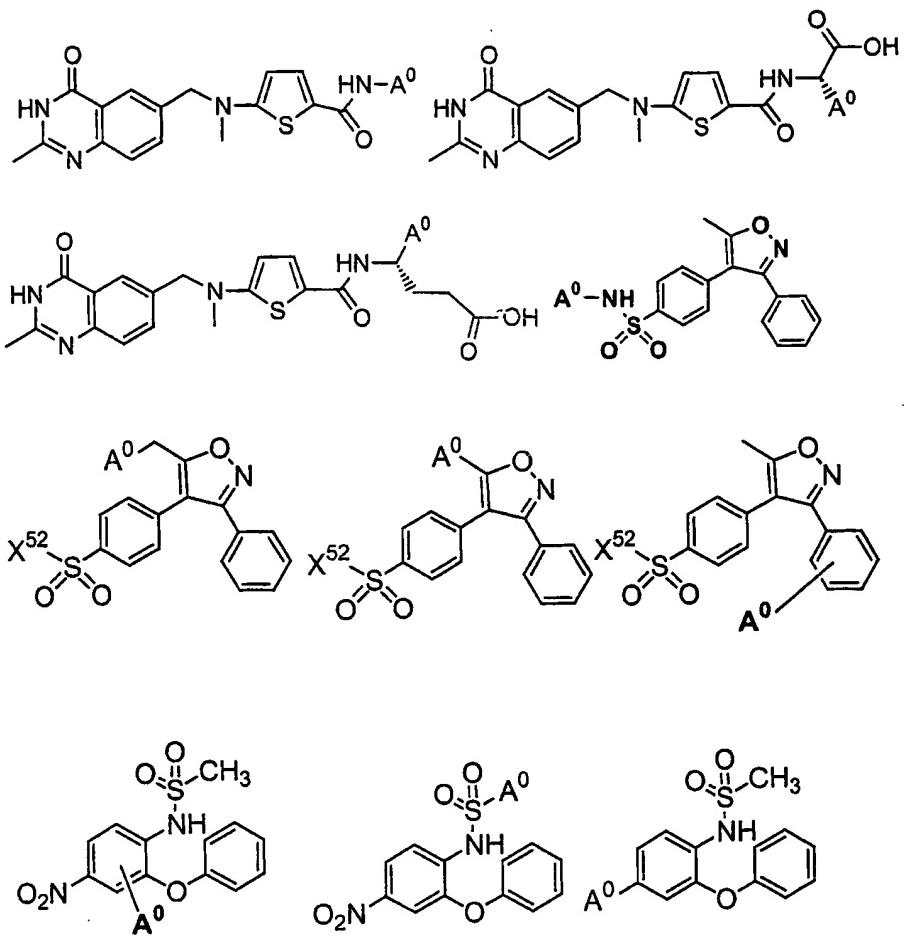
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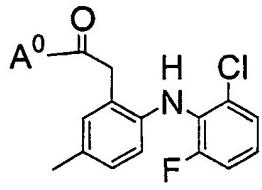
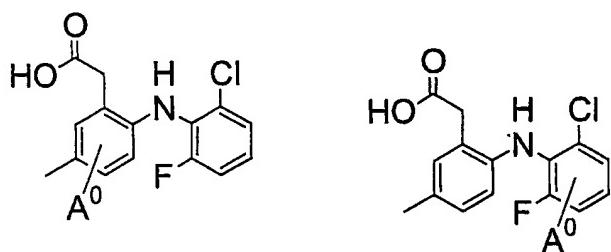
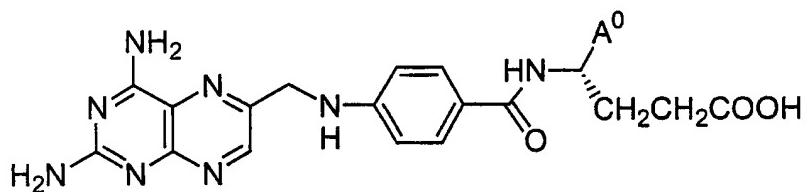
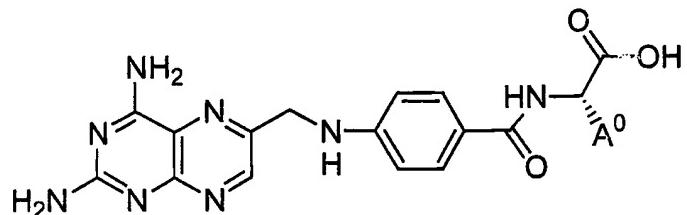
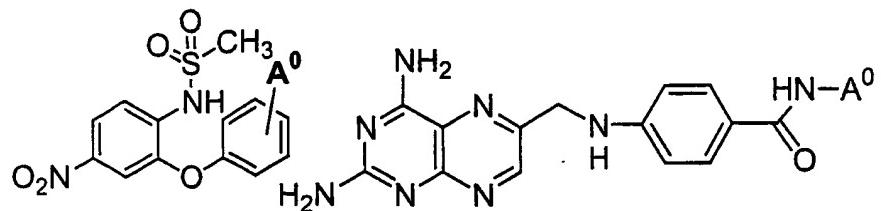


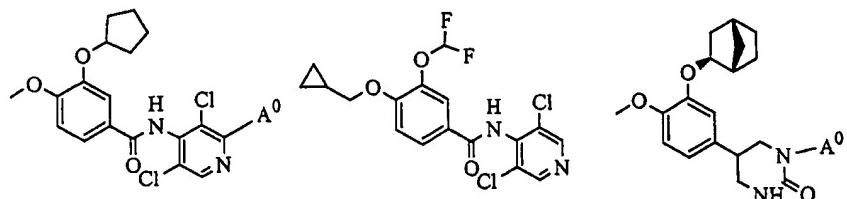
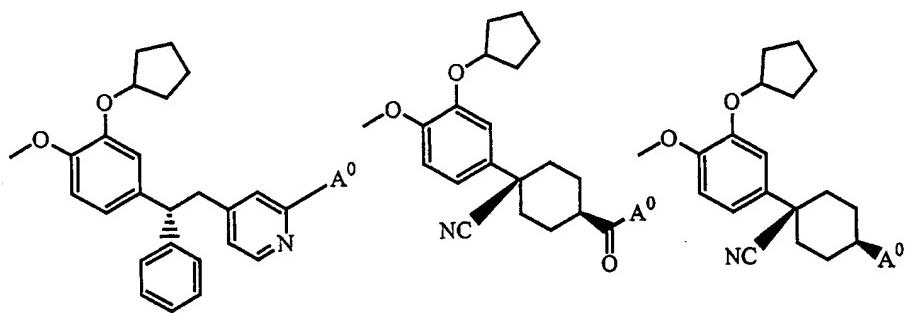
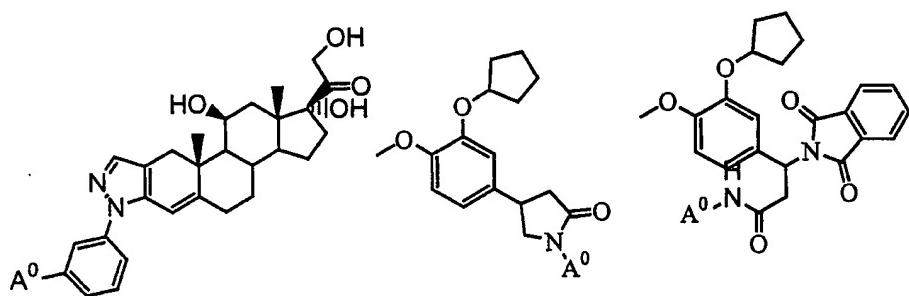
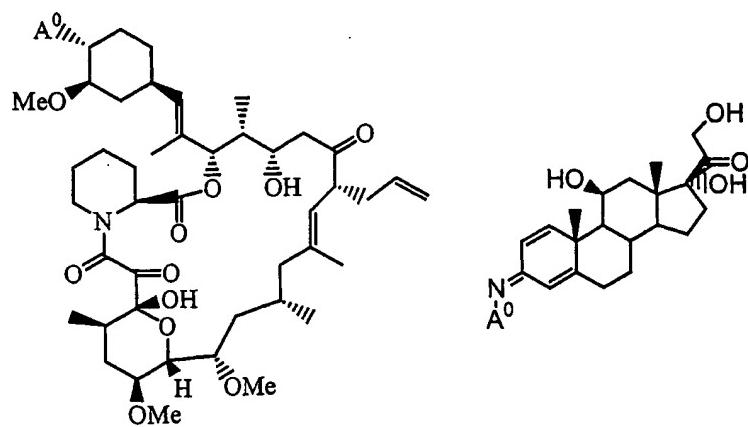


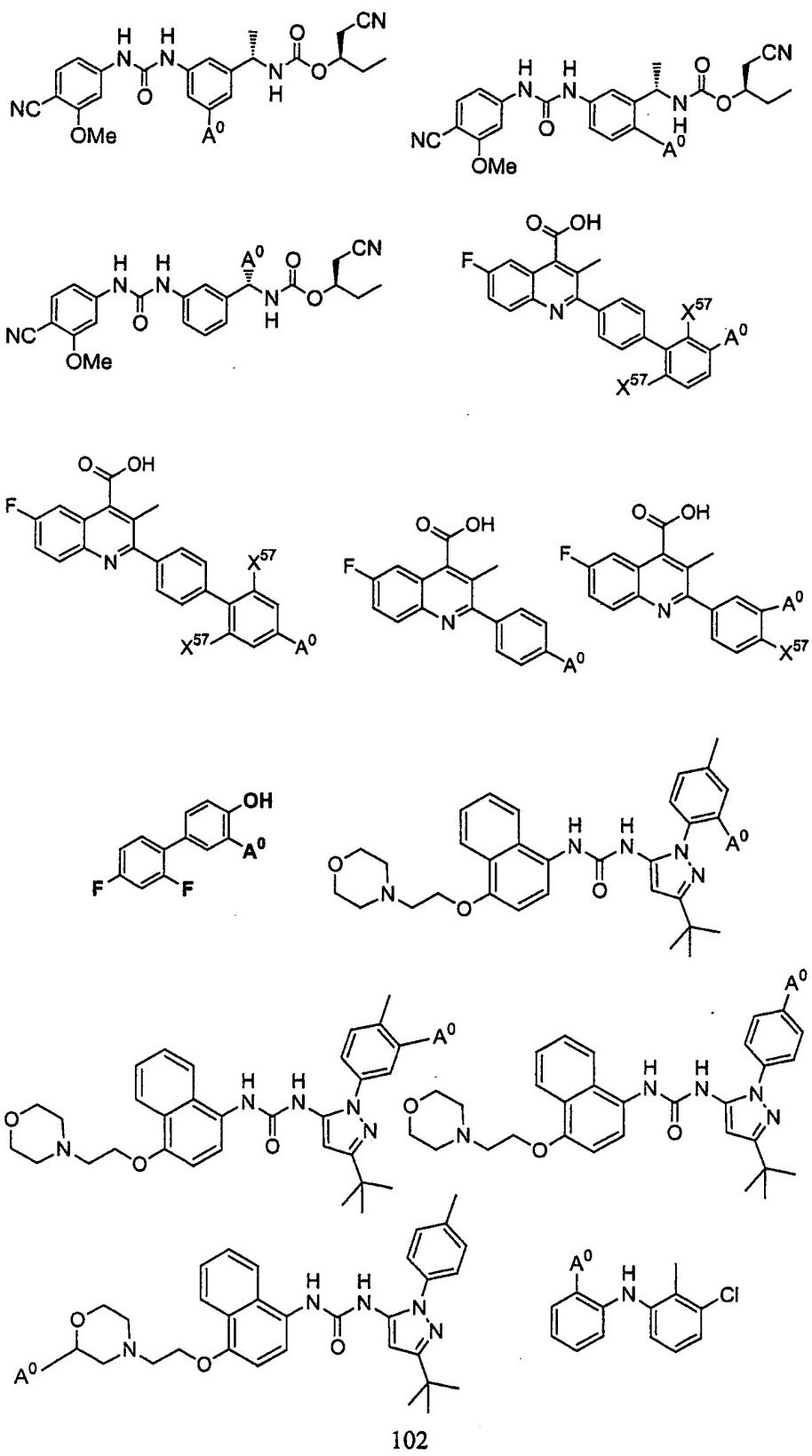


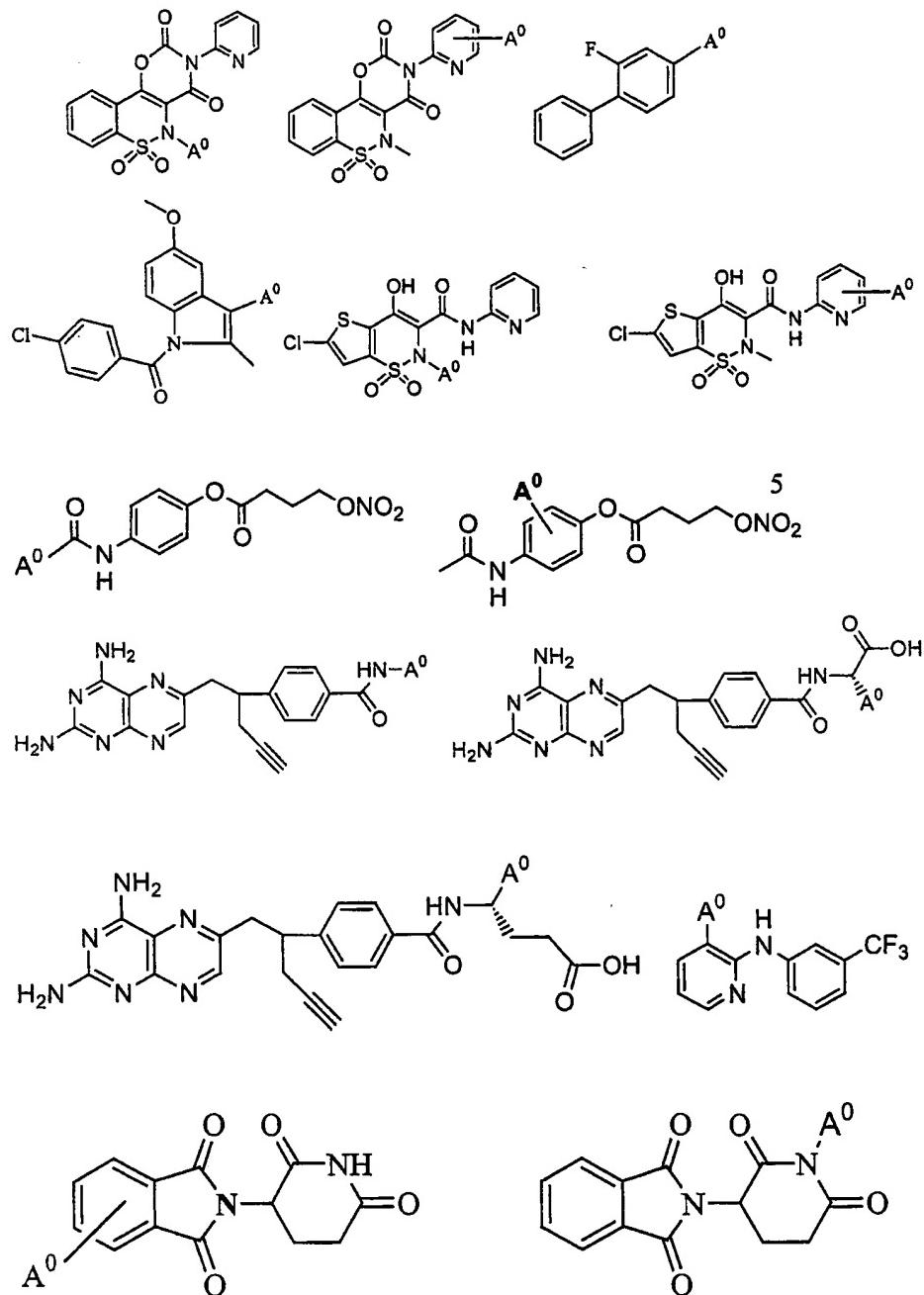


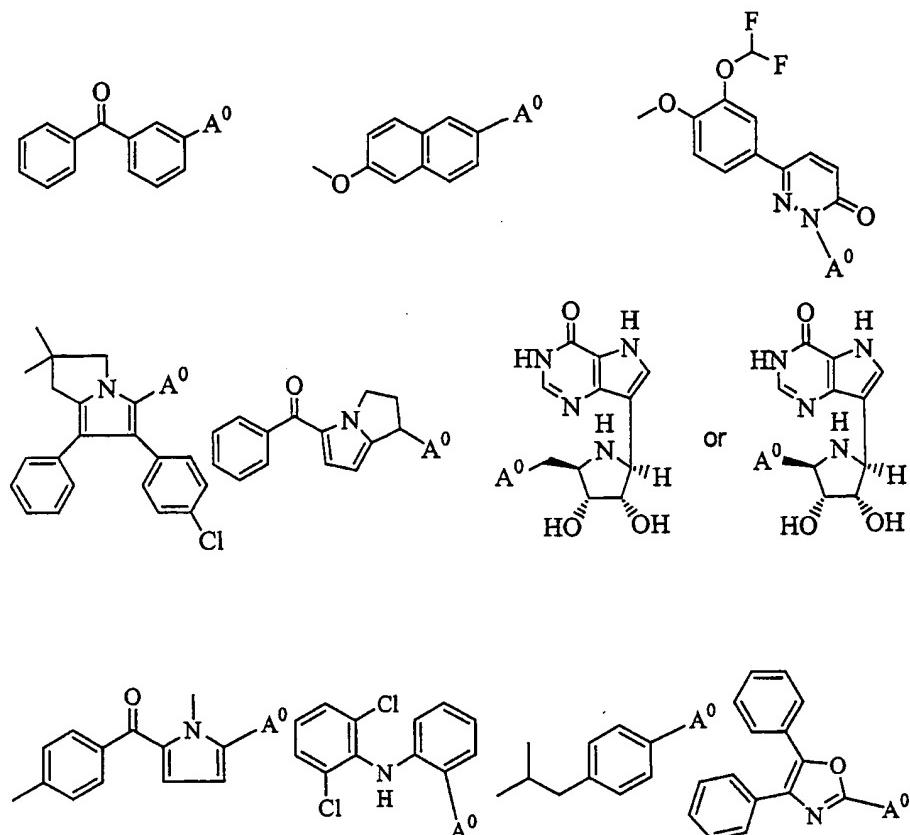




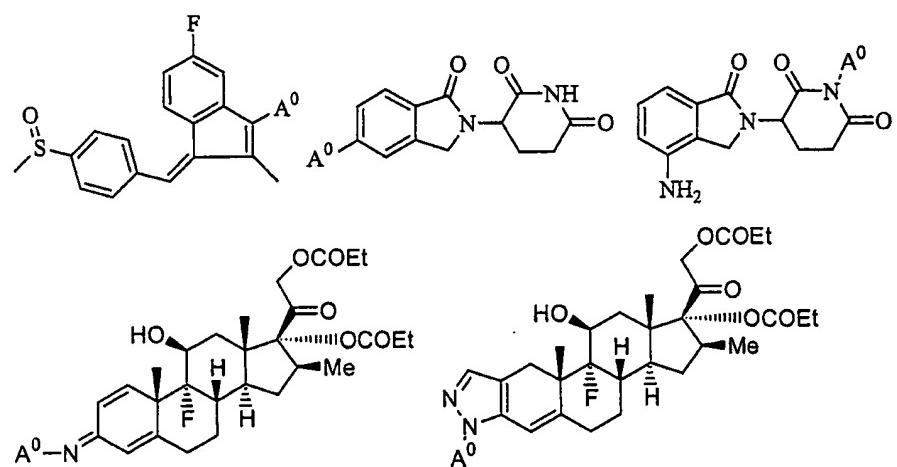


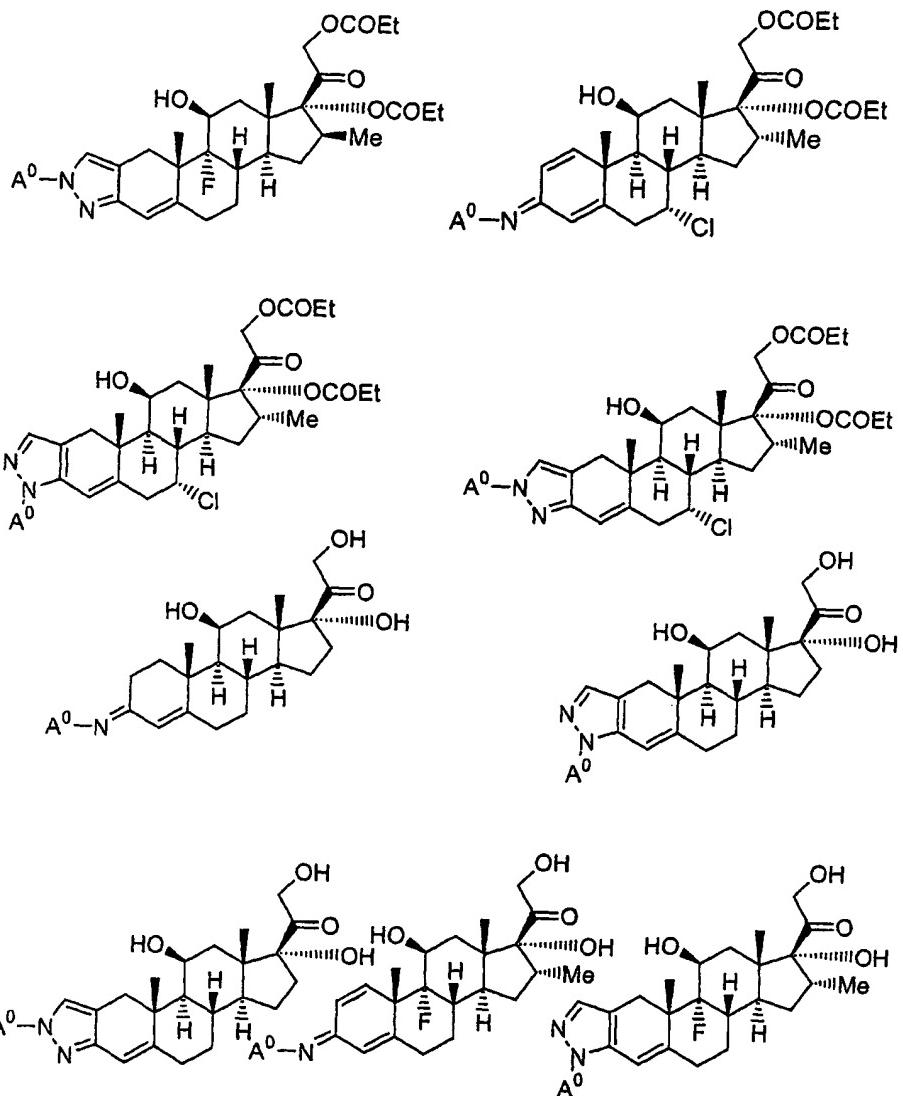


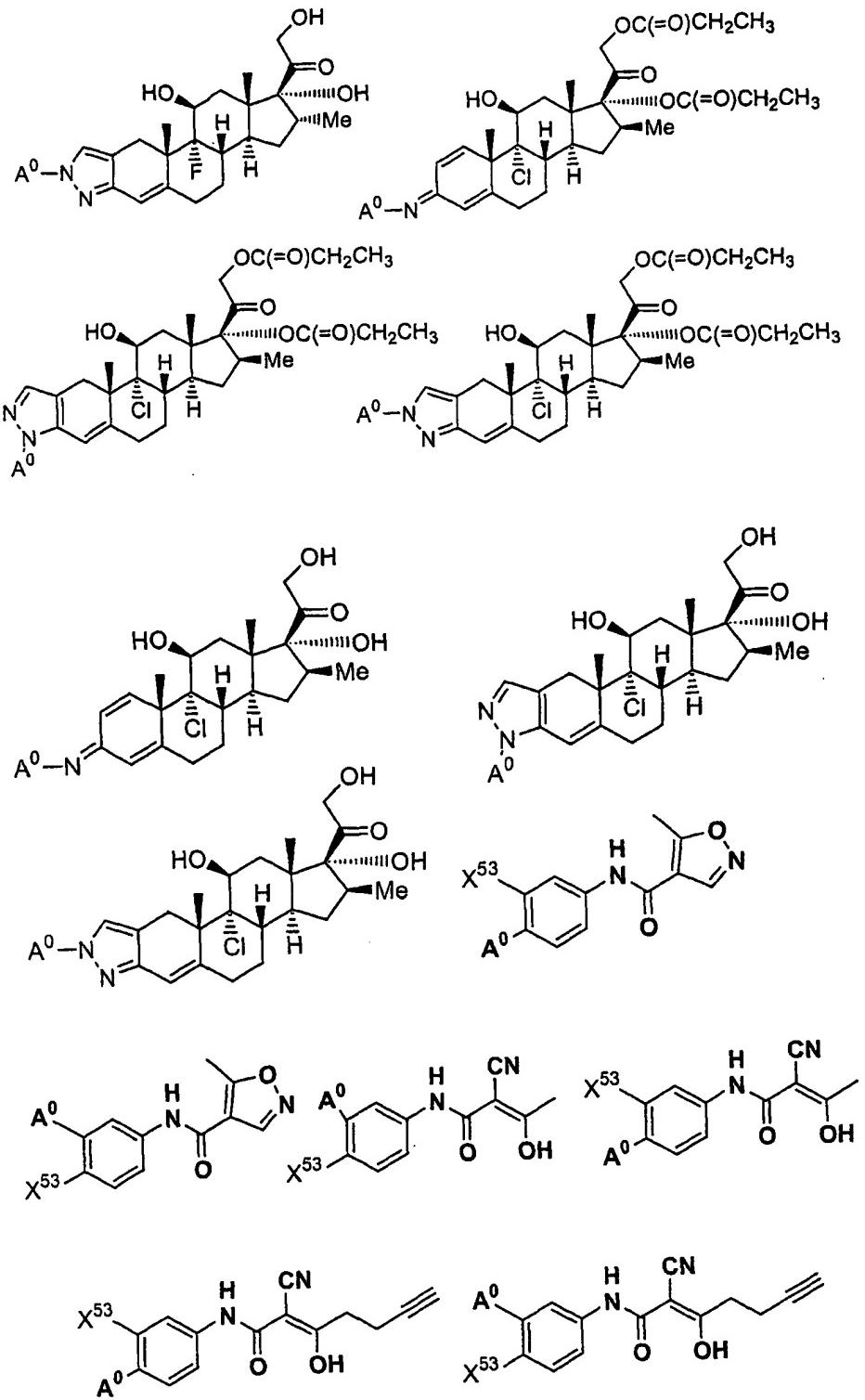


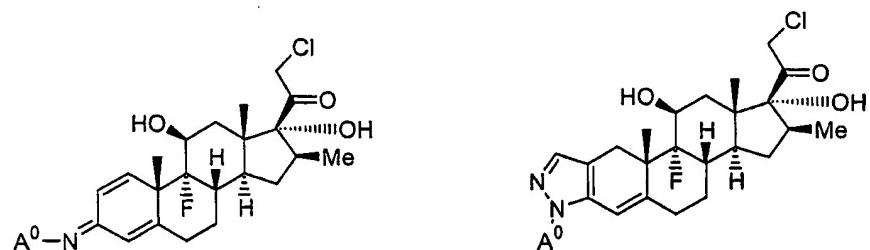
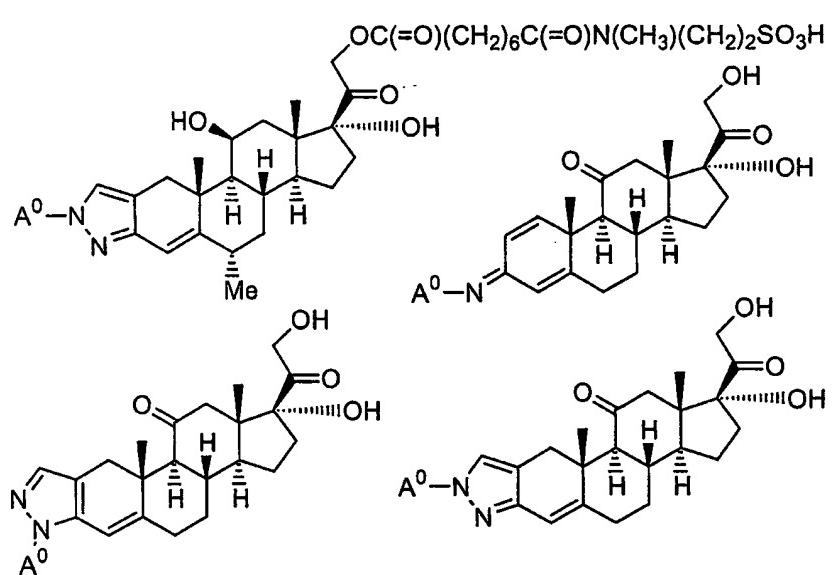
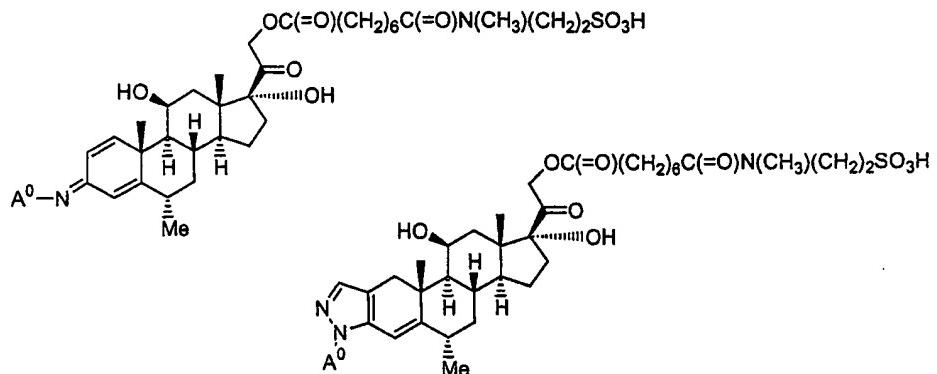


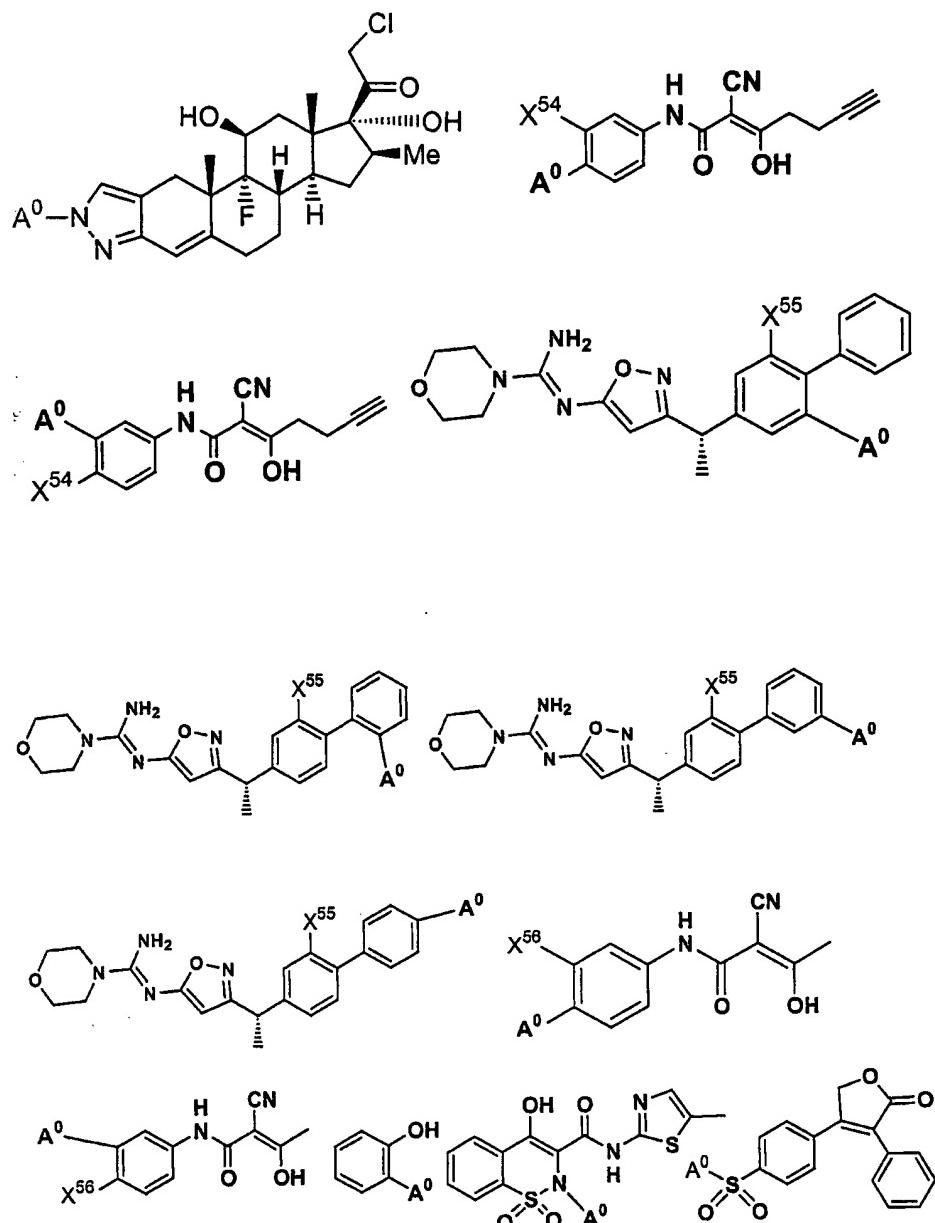
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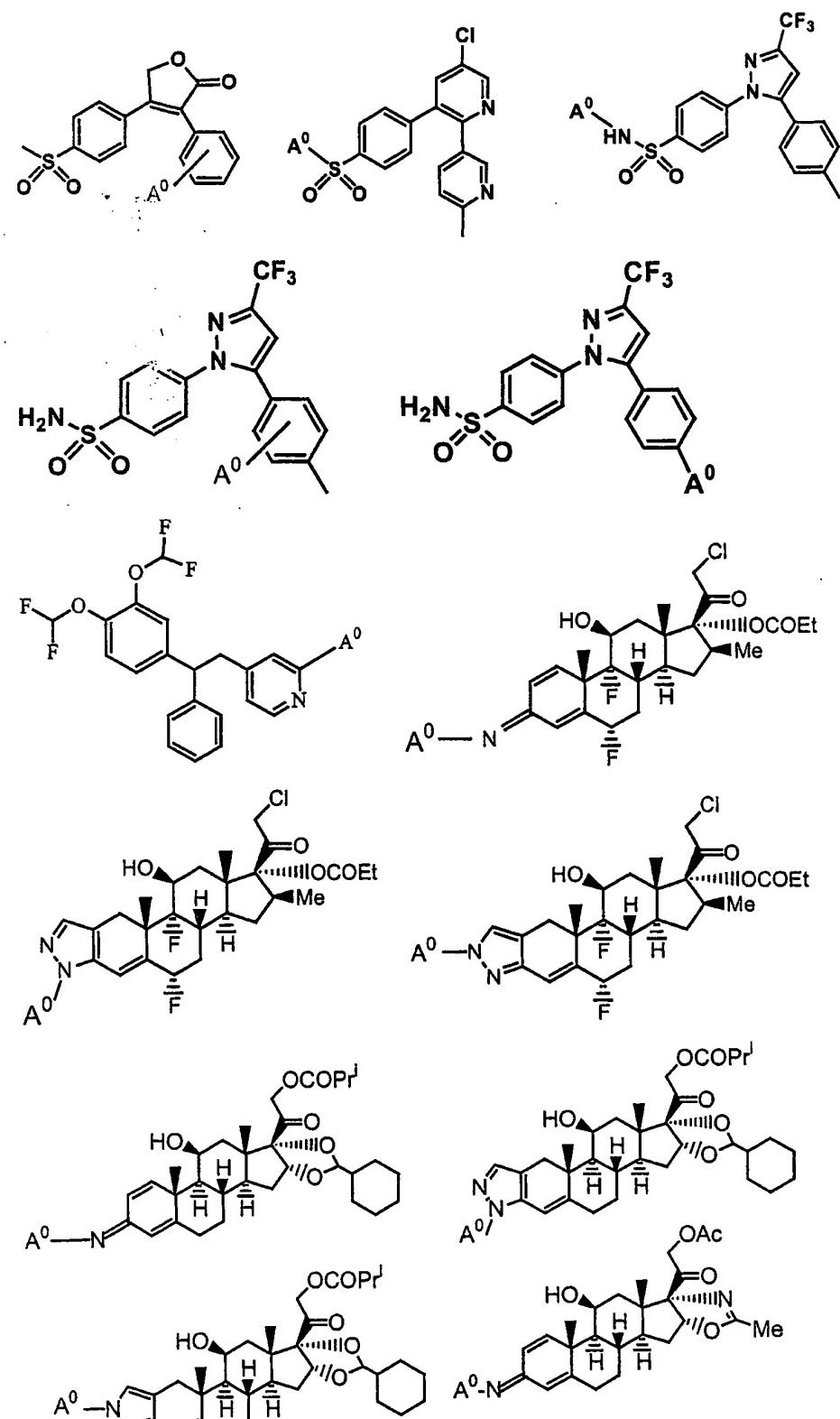


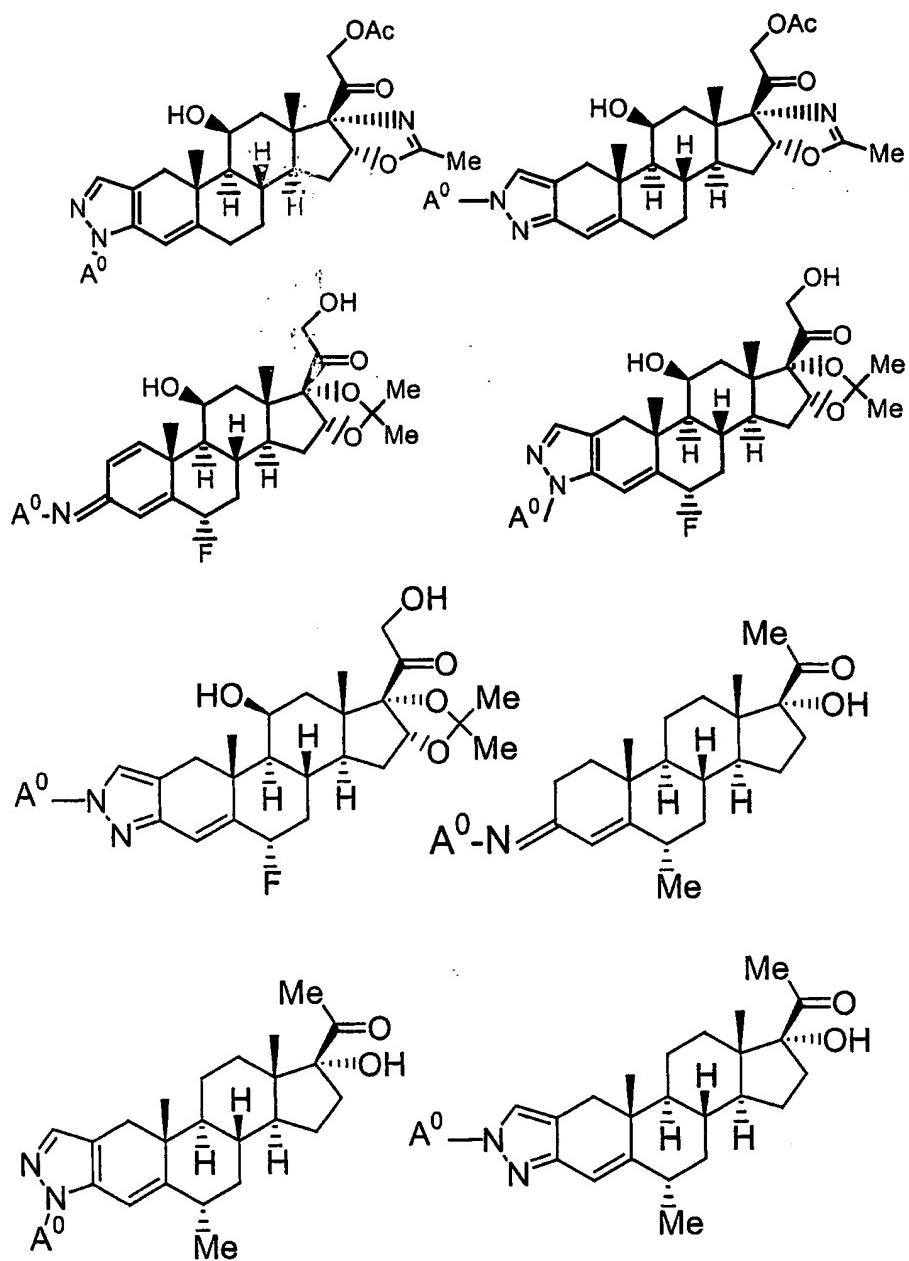


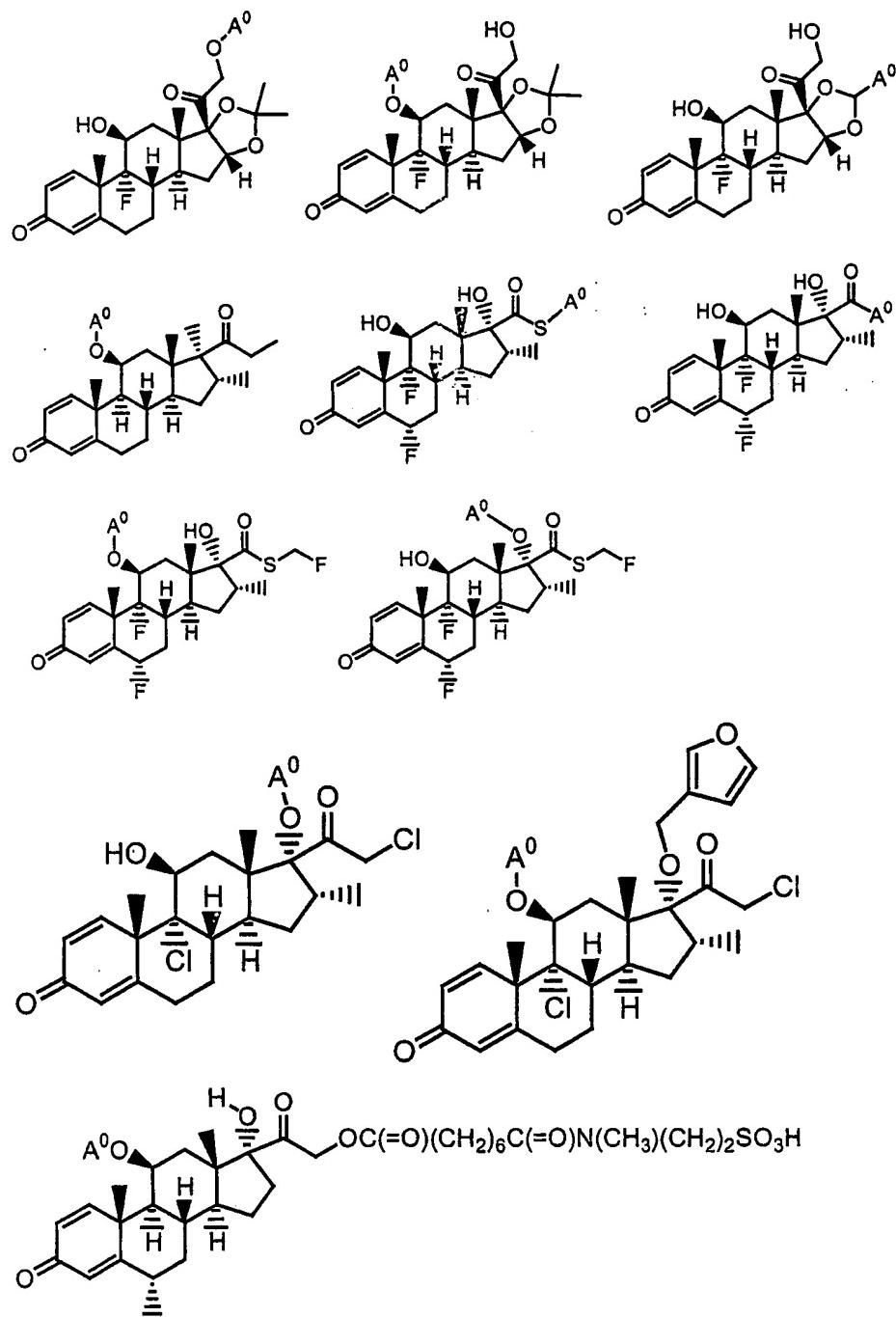


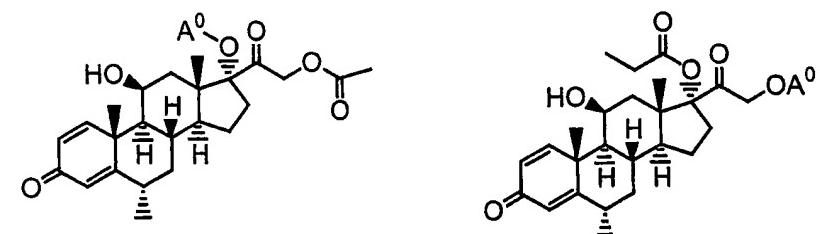
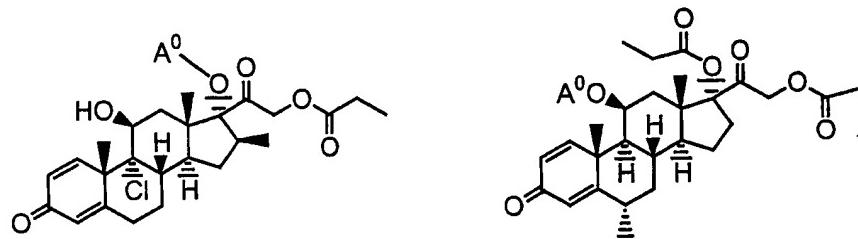
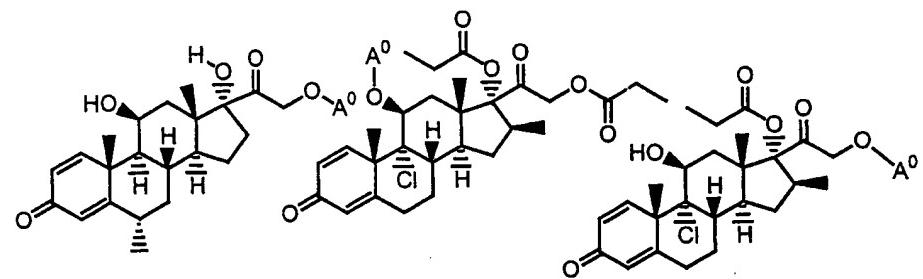
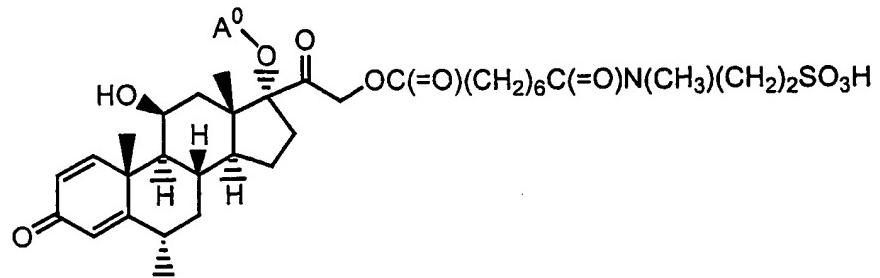


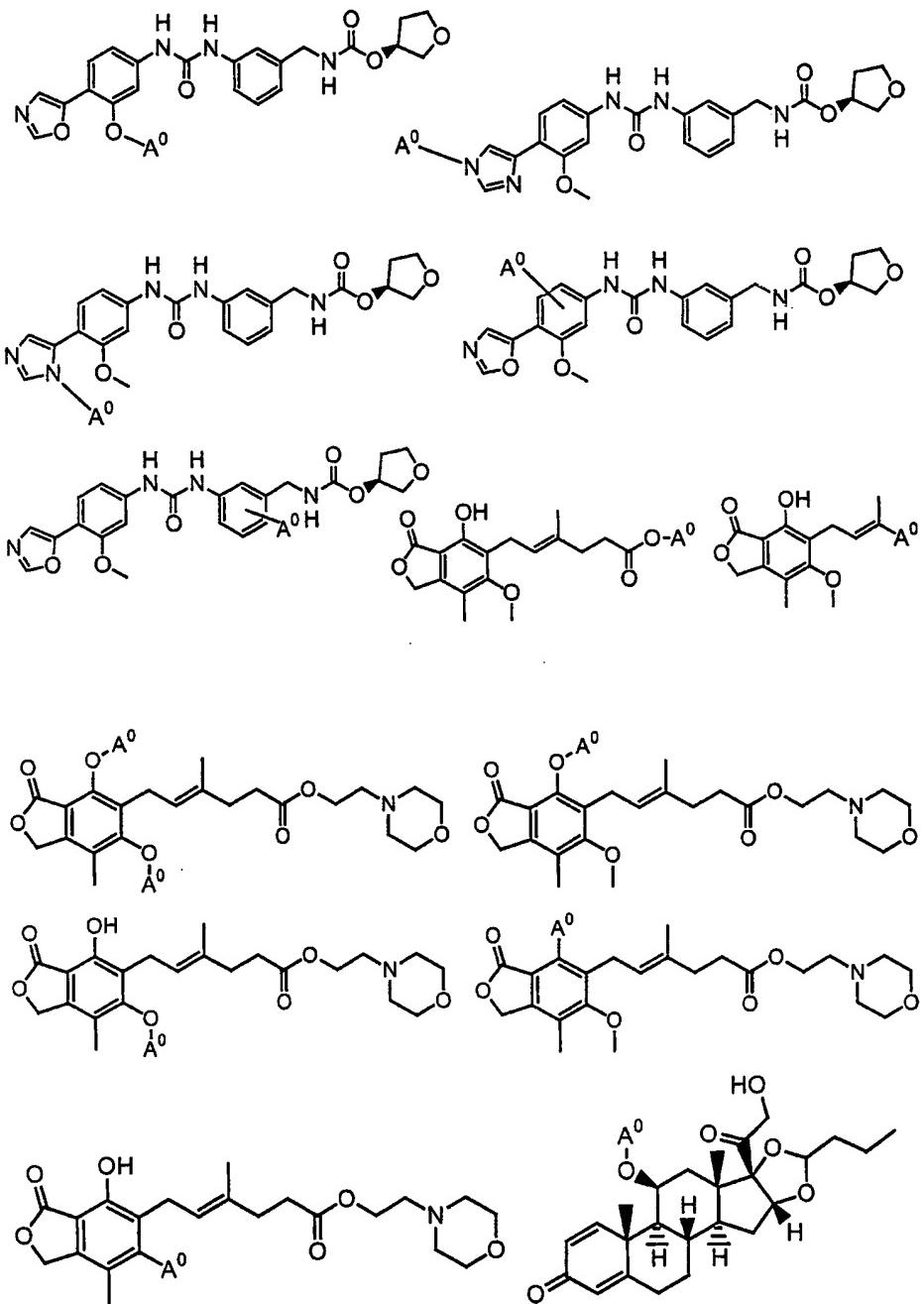


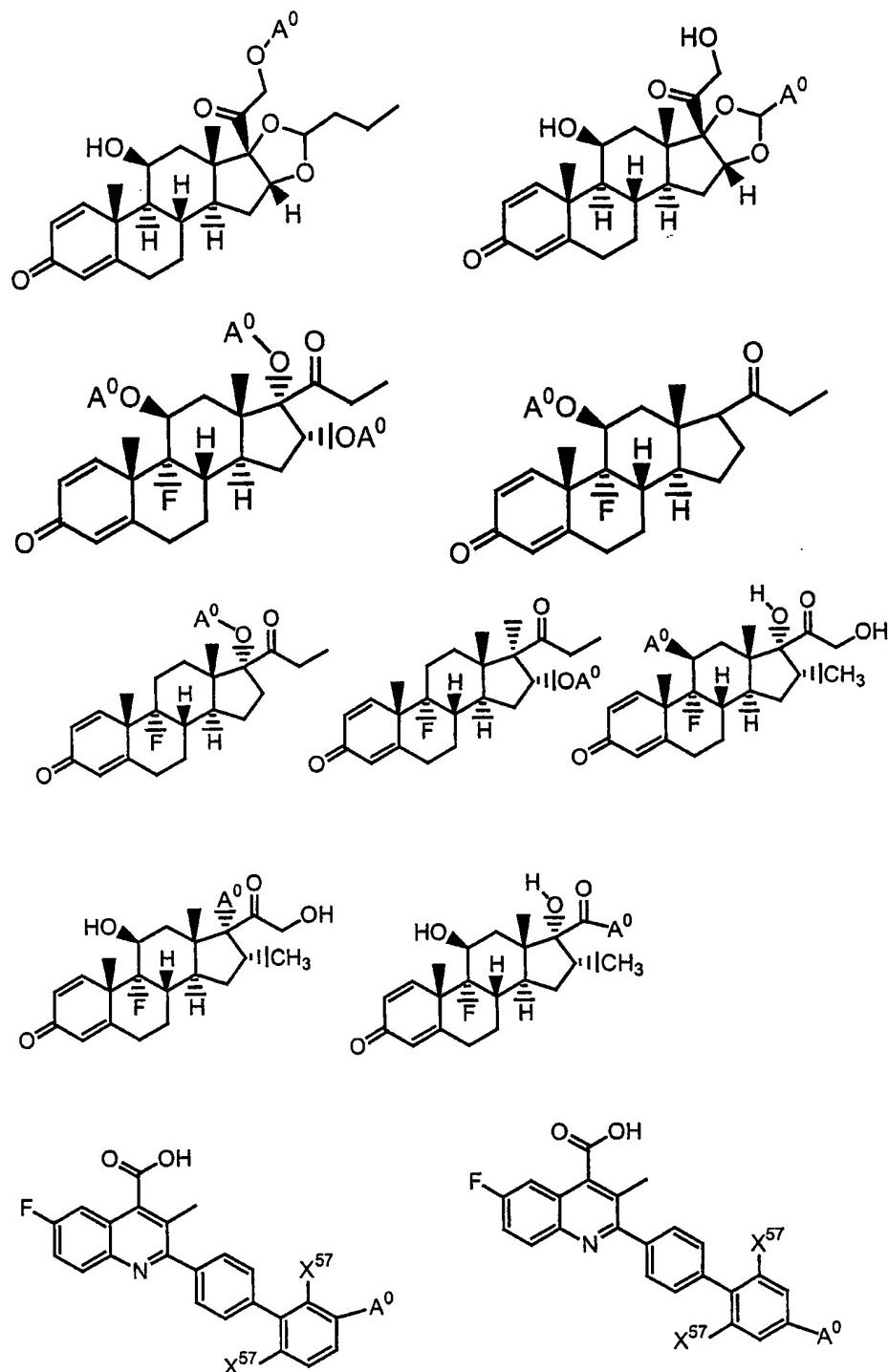


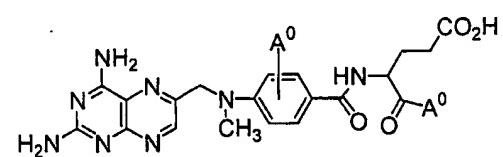
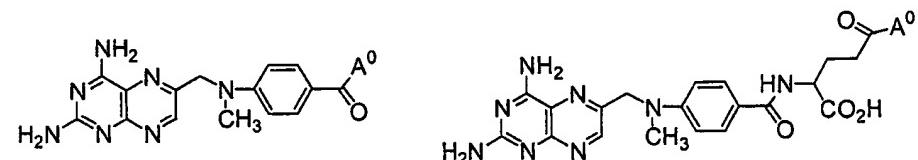
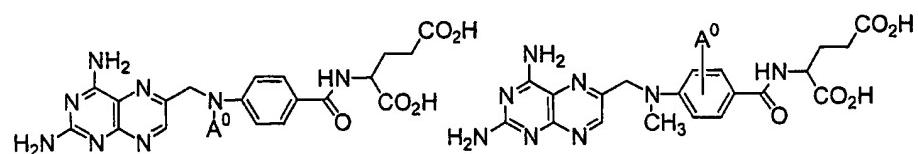
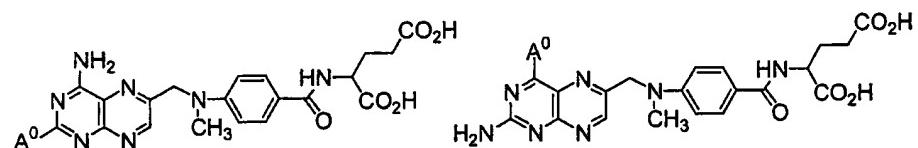
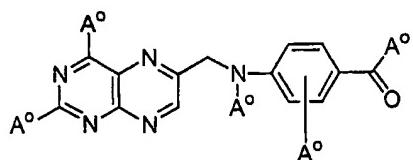
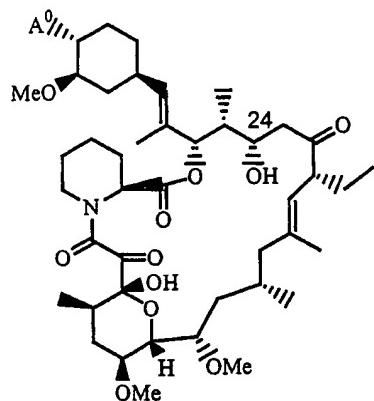
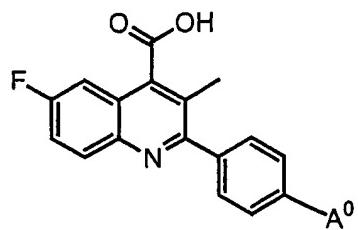
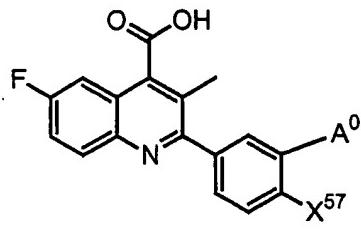


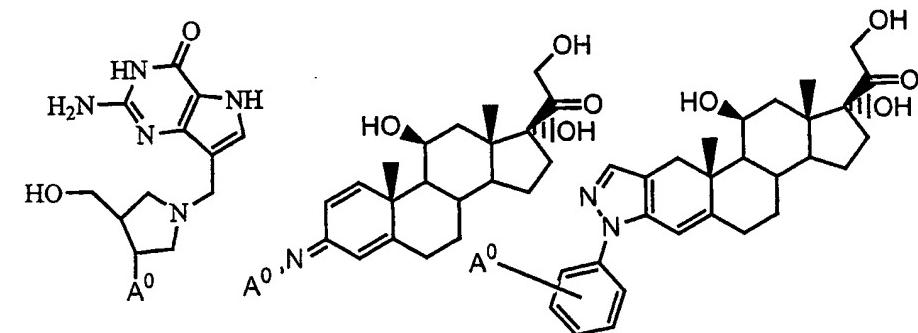
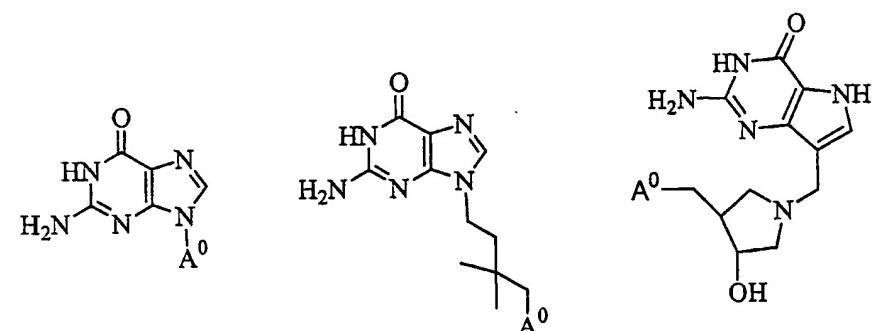
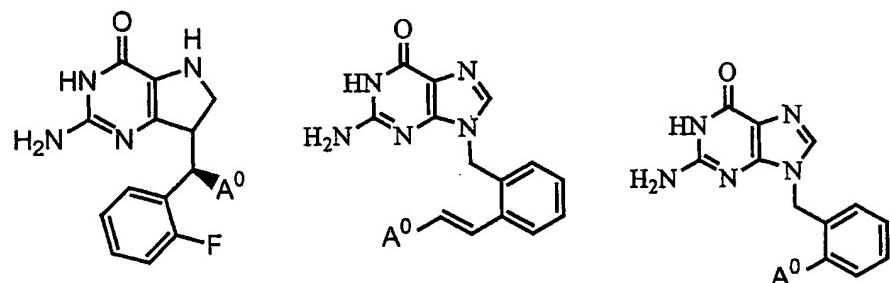
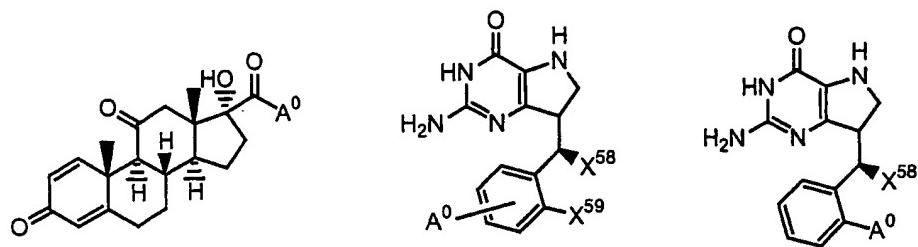


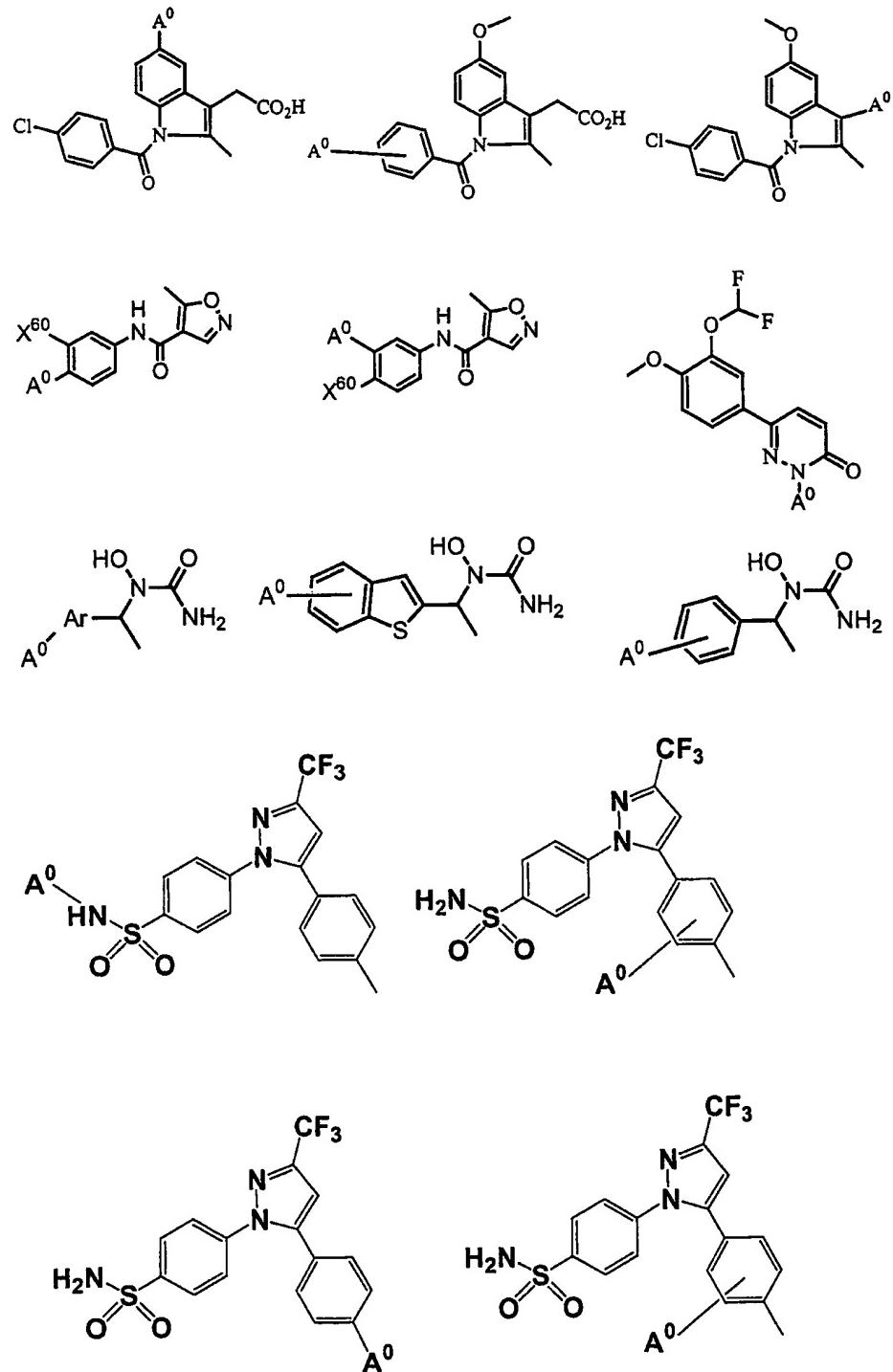


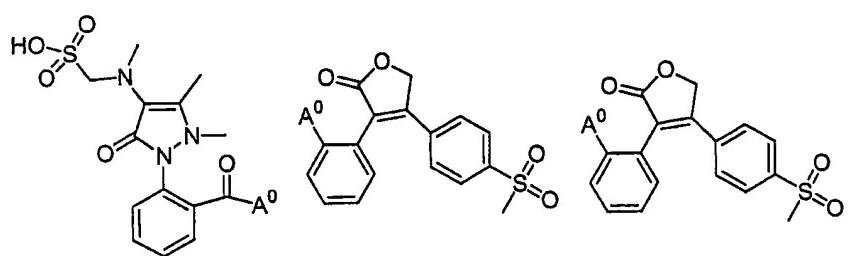
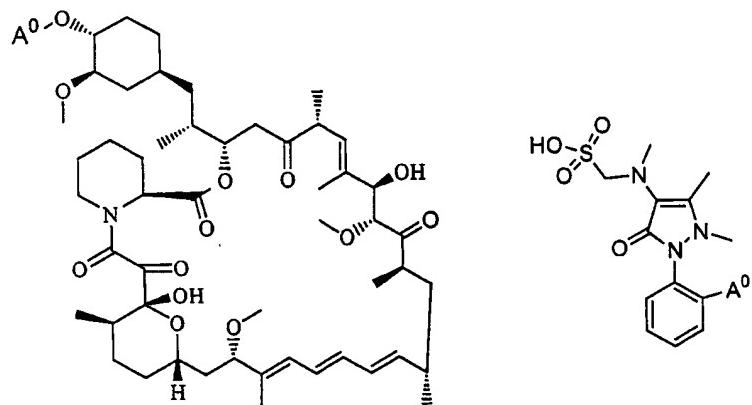
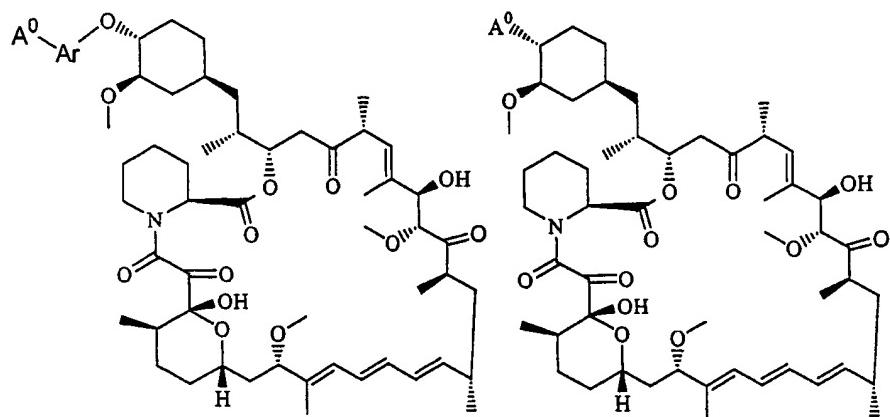


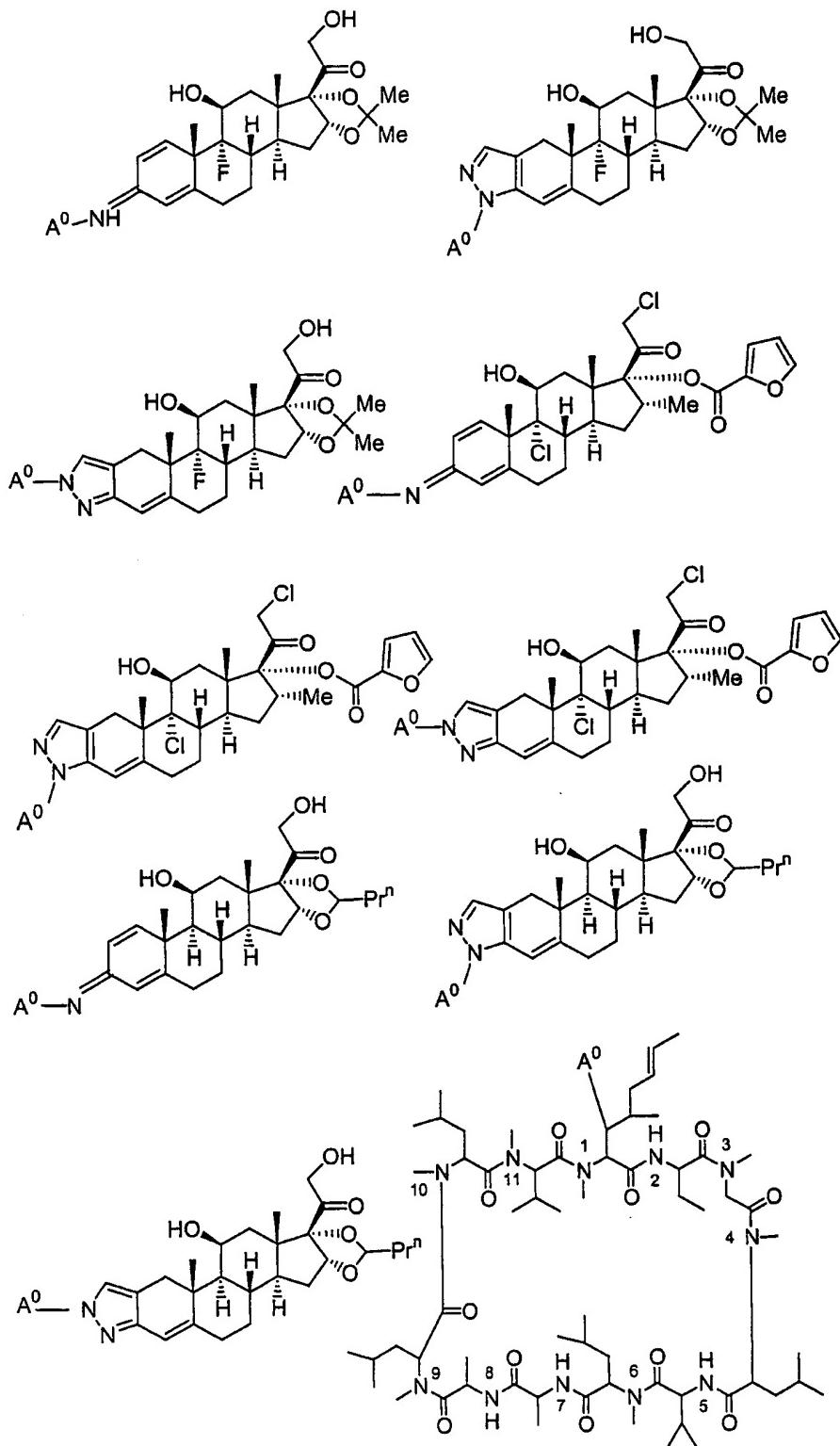


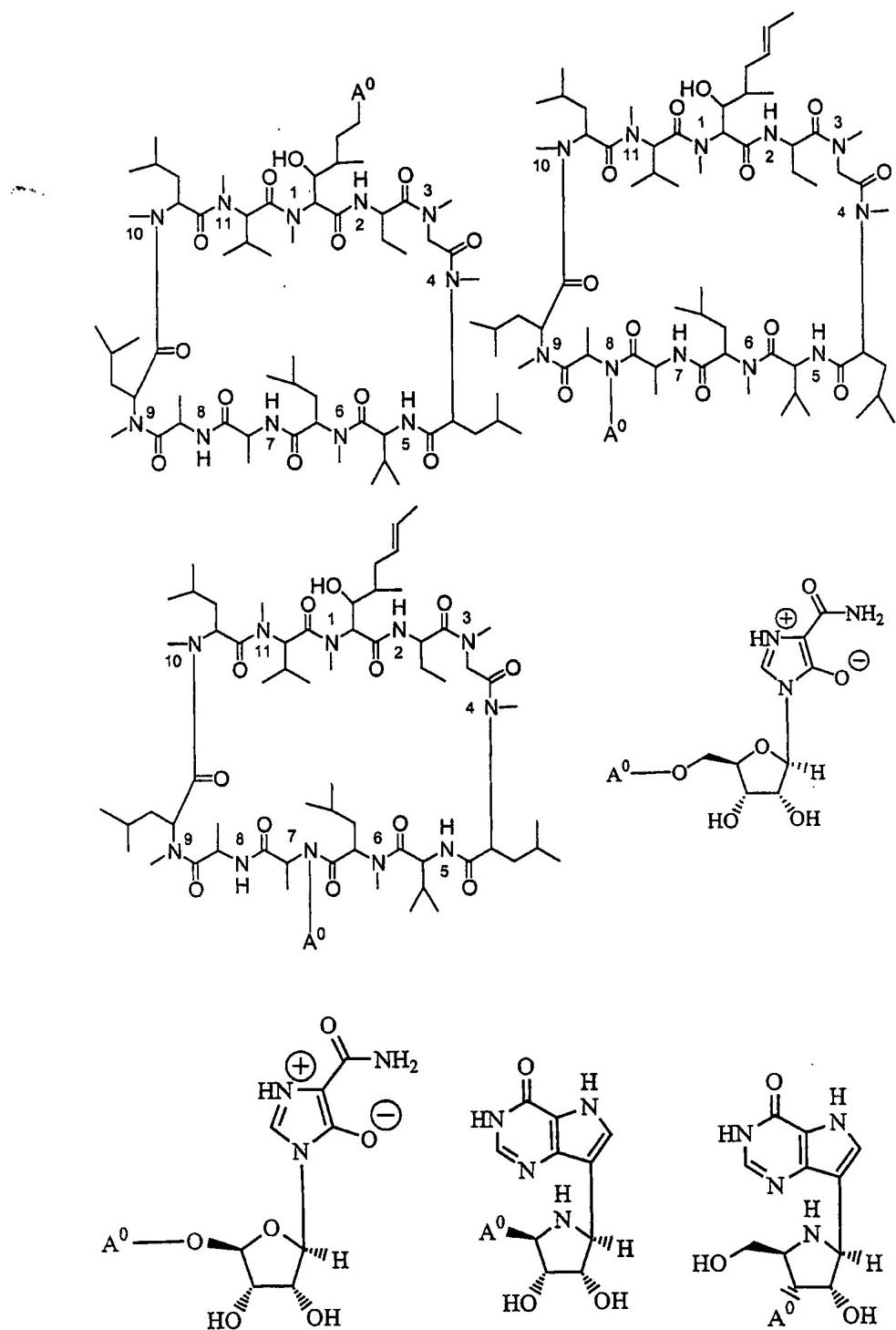


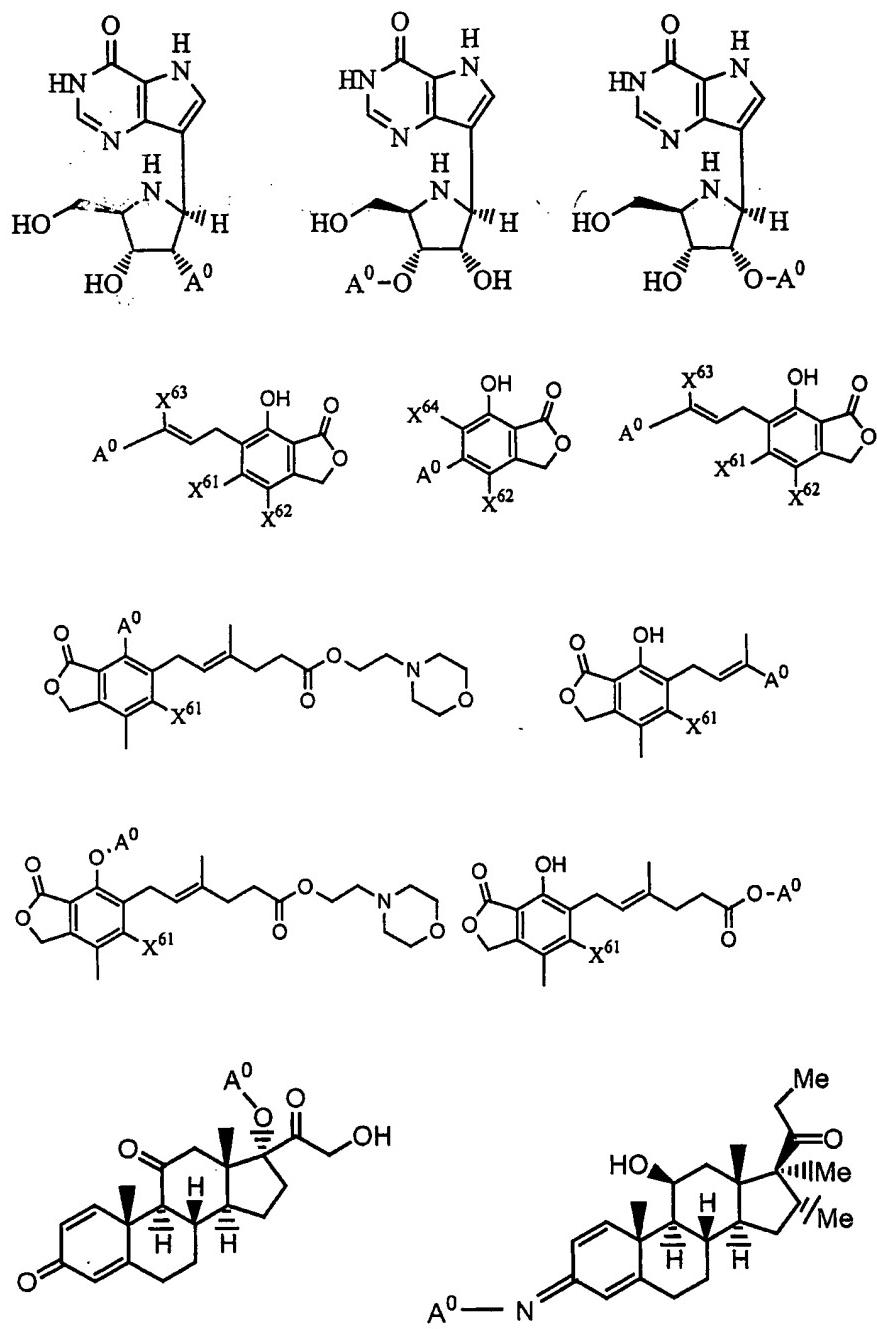




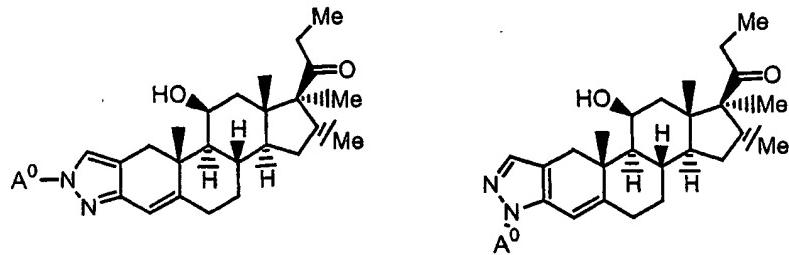








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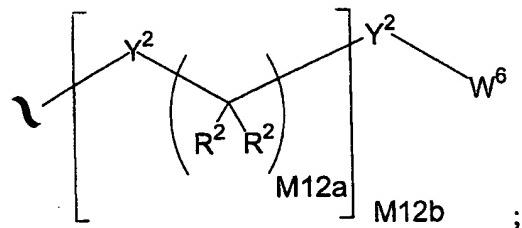


wherein:

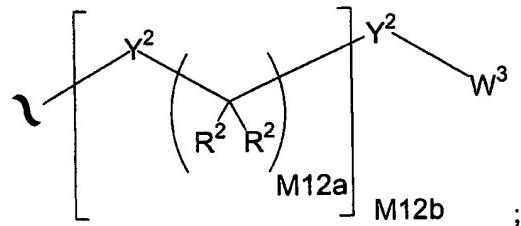
A^0 is A^1 , A^2 or W^3 with the proviso that one A^0 is A^1 ;

A^1 is:

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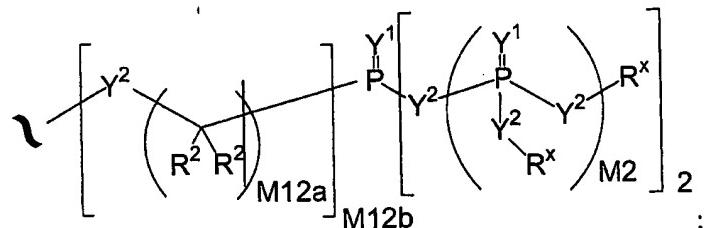


A^2 is:



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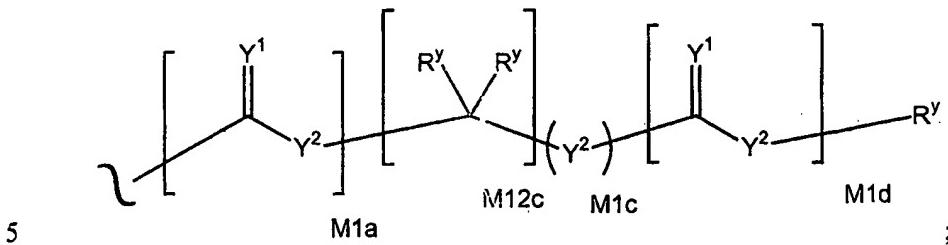
A^3 is:



Y^1 is independently O, S, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x), or
N(N(R^x))(R x));

Y^2 is independently a bond, O, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x), N(N(R^x))(R x)), -S(O) M_2 - or -S(O) M_2 -S(O) M_2 -; and when Y^2 joins two phosphorous atoms Y^2 can also be C(R^2)(R 2);

R^x is independently H, R 1 , R 2 , W 3 , a protecting group, or the formula:



wherein:

R^y is independently H, W 3 , R 2 or a protecting group;

R 1 is independently H or alkyl of 1 to 18 carbon atoms;

10 R 2 is independently H, R 1 , R 3 or R 4 wherein each R 4 is independently substituted with 0 to 3 R 3 groups or taken together at a carbon atom, two R 2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R 3 groups;

R 3 is R 3a , R 3b , R 3c or R 3d , provided that when R 3 is bound to a heteroatom, then R 3 is R 3c or R 3d ,

15 R 3a is F, Cl, Br, I, -CN, N₃ or -NO₂;

R 3b is Y 1 ;

R 3c is -R x , -N(R^x)(R x), -SR x , -S(O)R x , -S(O)₂R x , -S(O)(OR x), -S(O)₂(OR x), -OC(Y 1)R x , -OC(Y 1)OR x , -OC(Y 1)(N(R^x))(R x)), -SC(Y 1)R x , -SC(Y 1)OR x , -SC(Y 1)(N(R^x))(R x)), -N(R^x)C(Y 1)R x , -N(R^x)C(Y 1)OR x , or -

20 N(R^x)C(Y 1)(N(R^x))(R x)) ;

R 3d is -C(Y 1)R x , -C(Y 1)OR x or -C(Y 1)(N(R^x))(R x));

R 4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R 5 is R 4 wherein each R 4 is substituted with 0 to 3 R 3 groups;

25 R 5a is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R 3 groups;

W 3 is W 4 or W 5 ;

W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

5 $M2$ is 0, 1 or 2;

$M12a$ is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

$M12b$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

$M1a$, $M1c$, and $M1d$ are independently 0 or 1;

$M12c$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

10 X^{50} is H or F;

X^{51} is H, hydroxy, or acyloxy;

X^{52} is NH_2 or $EtC(O)N-Na^+$;

X^{53} is H, methyl, CF_3 , or halo;

X^{54} is H, halo, trifluoromethyl, (C1-C3)alkyl, cyano, or (C1-C3)alkoxy;

15 X^{55} is H, F, Cl, Br, methyl, or trifluoromethyl;

X^{56} is hydrogen, halo, trifluoromethyl, cyano, methyl;

X^{57} is H, F, Cl, CF_3 , cyano, methyl, or *t*-butyl;

X^{58} is H or CH_2OH ;

X^{59} is H or F;

20 X^{60} is H, trifluoromethyl, or cyano;

X^{61} is methoxy, ethoxy, propoxy, difluoromethoxy, trifluoromethoxy, vinyl, ethyl, methyl, propyl, butyl, cyclopropyl, N-methylamino, or N-formylamino;

X^{62} is methyl, chloro, or trifluoromethyl;

25 X^{63} is H, methyl, ethyl, cyclopropyl, vinyl, or trifluoromethyl;

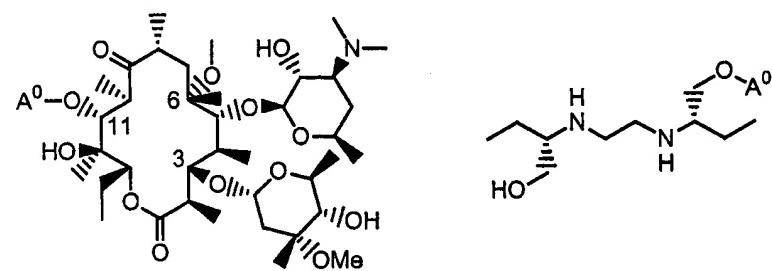
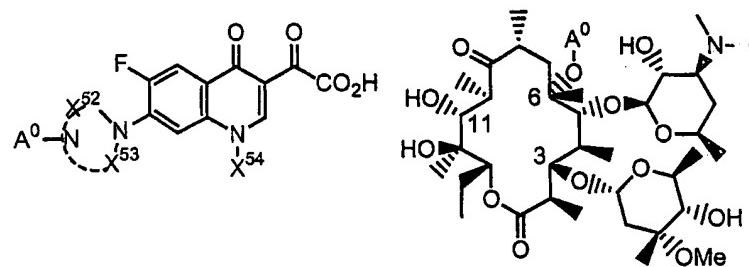
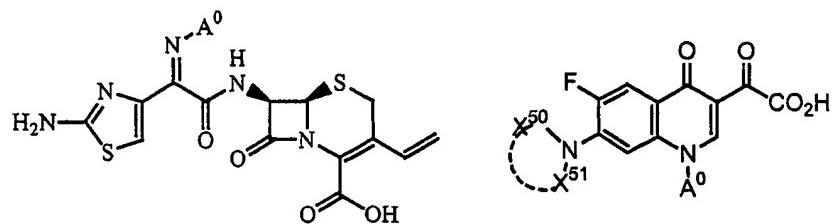
X^{64} is H, methyl, ethyl, cyclopropyl, chloro, vinyl, allyl, 3-methyl-1-butene-1-yl;

X^{65} is H or F; and

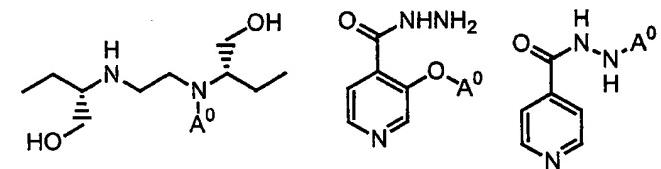
Ar is aryl or heteroaryl.

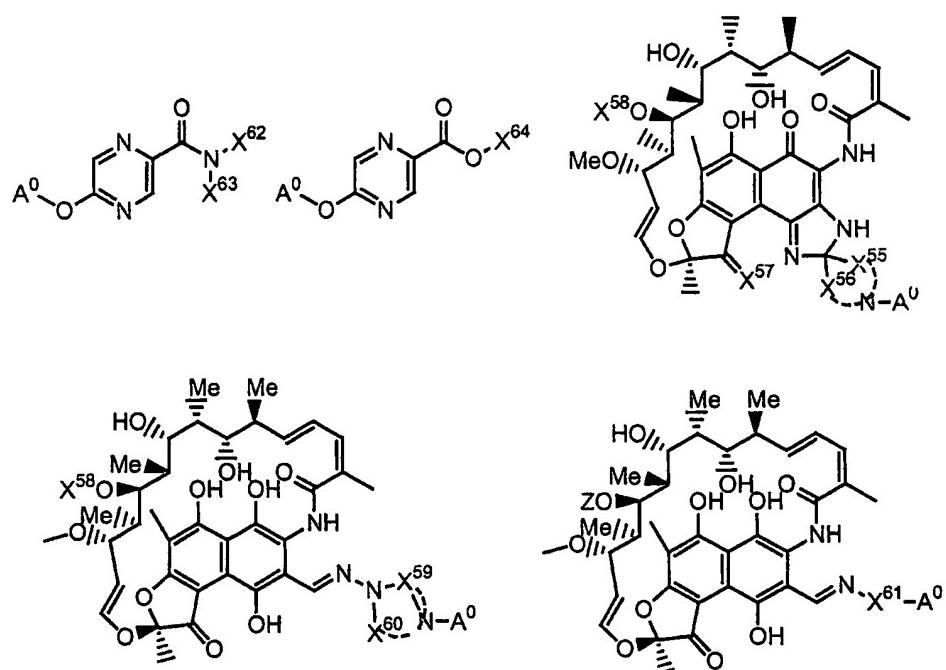
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In another embodiment the invention provides a conjugate, which has any one of the following formulae:



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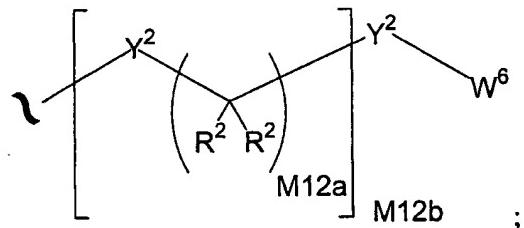




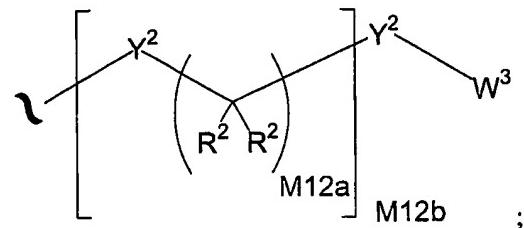
wherein:

A^0 is A^1 , A^2 or W^3 with the proviso that one A^0 is A^1 ;

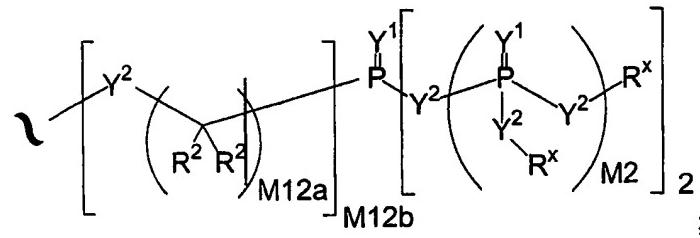
5 A^1 is:



A^2 is:



10 A^3 is:

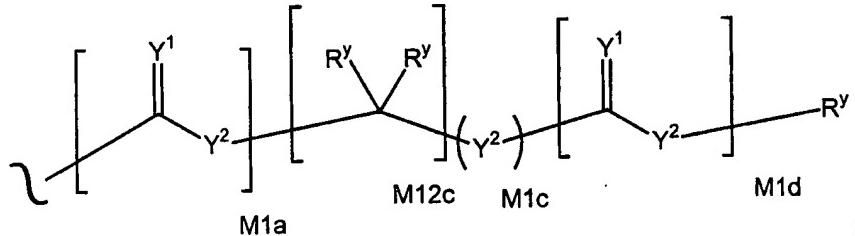


Y^1 is independently O, S, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x), or

N(N(R^x))(R x);

5 Y^2 is independently a bond, O, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x),
N(N(R^x))(R x), -S(O) $M2-$, or -S(O) $M2$ -S(O) $M2$; and when Y^2 joins two
phosphorous atoms Y^2 can also be C(R^2)(R 2);

R^x is independently H, R 1 , R 2 , W 3 , a protecting group, or the formula:



10 wherein:

R^y is independently H, W 3 , R 2 or a protecting group;

R 1 is independently H or alkyl of 1 to 18 carbon atoms;

15 R 2 is independently H, R 1 , R 3 or R 4 wherein each R 4 is independently
substituted with 0 to 3 R 3 groups or taken together at a carbon atom, two R 2

groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3
R 3 groups;

R 3 is R 3a , R 3b , R 3c or R 3d , provided that when R 3 is bound to a
heteroatom, then R 3 is R 3c or R 3d ;

R 3a is F, Cl, Br, I, -CN, N₃ or -NO₂;

20 R 3b is Y 1 ;

R 3c is -R x , -N(R^x)(R x), -SR x , -S(O)R x , -S(O)₂R x , -S(O)(OR x), -
S(O)₂(OR x), -OC(Y 1)R x , -OC(Y 1)OR x , -OC(Y 1)(N(R^x)(R x)), -SC(Y 1)R x , -
SC(Y 1)OR x , -SC(Y 1)(N(R^x)(R x)), -N(R^x)C(Y 1)R x , -N(R^x)C(Y 1)OR x , or -
N(R^x)C(Y 1)(N(R^x)(R x));

- R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x))(R^x)$;
- R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;
- R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;
- 5 R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;
- W^3 is W^4 or W^5 ;
- W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;
- 10 W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;
- W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;
- $M2$ is 0, 1 or 2;
- $M12a$ is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- 15 $M12b$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- $M1a$, $M1c$, and $M1d$ are independently 0 or 1;
- $M12c$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- 20 X^{50} and X^{51} are alkyl groups which may or may not be linked to each other to form a ring as shown by the dotted curve, which alkyl groups may optionally be substituted intra-chain with one or more heteroatoms such as nitrogen and oxygen, or in a pendant manner with one or more nitrogen, oxygen, or halogen;
- X^{52} and X^{53} are alkyl groups which may or may not be connected covalently to form a ring; if they do form a ring they are substituted with at least one heteroatom such as nitrogen, either within the chain (intra-chain) or in a pendant manner, which can serve as a handle for the linkage to the phosphonate moiety; if X^{52} and X^{53} do not form a ring, either or both may be substituted with heteroatoms such as N, O or halogen, wherein one of those heteroatoms, preferably nitrogen, can be used as a point of attachment to A^0 ;
- 25 X^{54} is any alkyl, aryl or aralkyl group;
- X^{56} and X^{55} are alkyl groups which may be linked to each other to form a ring as shown by the dotted curve, which ring is substituted either in a pendant

manner or within the ring itself with a heteroatom; or if X^{56} and X^{55} are not linked together, at least one of X^{56} and X^{55} is a heteroatom-substituted alkyl group and the other is an alkyl group or a heteroatom-substituted alkyl group, wherein one of X^{56} and X^{55} is linked to A^0 ;

5 X^{57} is oxo (=O), thioxo (=S), or hydroxy (-OH), provided when X^{57} is hydroxy, the second valence on the ring is occupied by H);

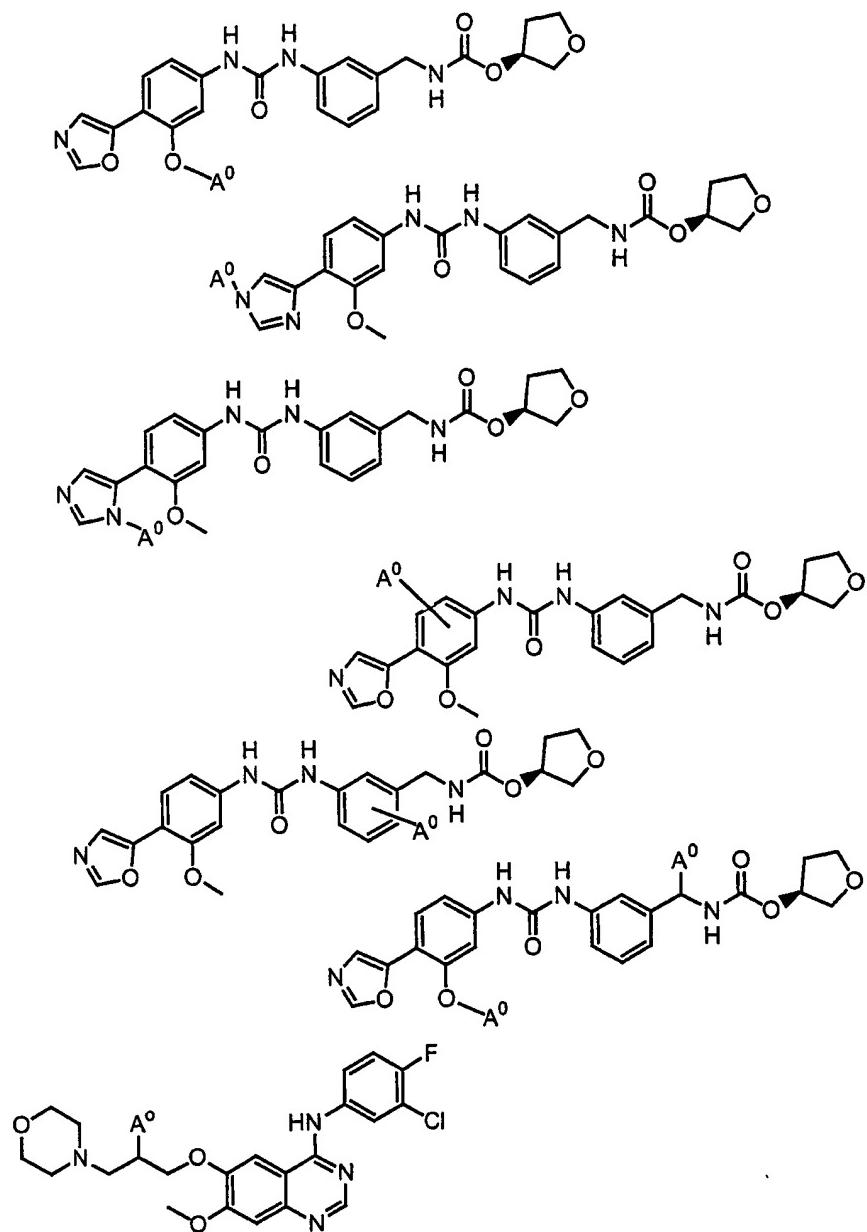
X^{58} is H, formyl, or acetyl;

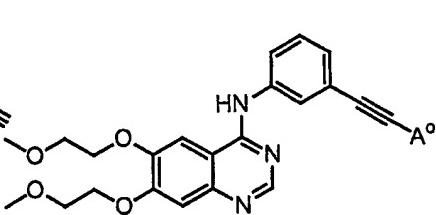
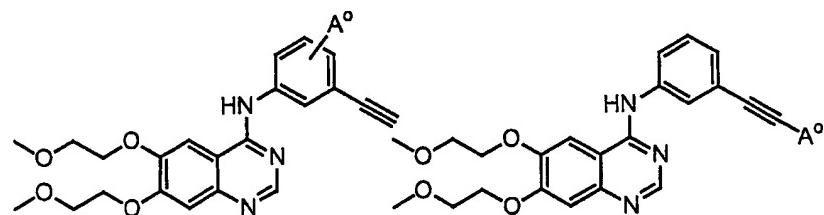
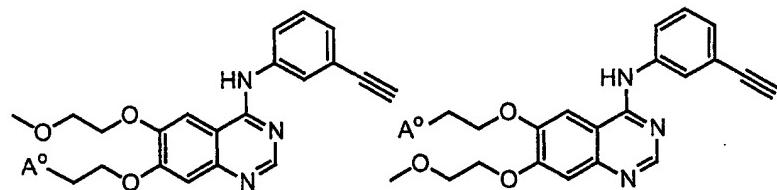
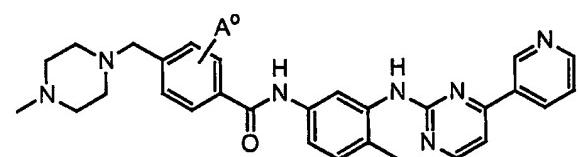
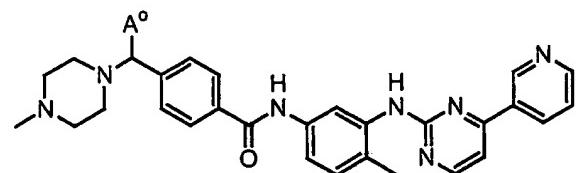
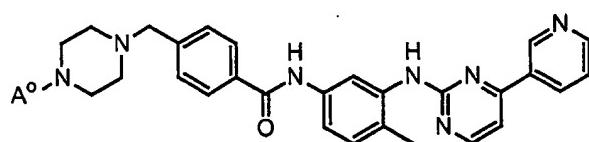
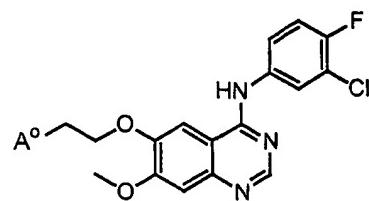
X^{59} and X^{60} are alkyl groups which may be linked to each other to form a ring as shown by the dotted curve, which ring is substituted either in a pendant manner or within the ring itself with a heteroatom; or if X^{59} and X^{60} are not linked together, at least one of X^{59} and X^{60} is a heteroatom-substituted alkyl group and the other is an alkyl group or a heteroatom-substituted alkyl group, wherein one of X^{59} and X^{60} is linked to A^0 ;

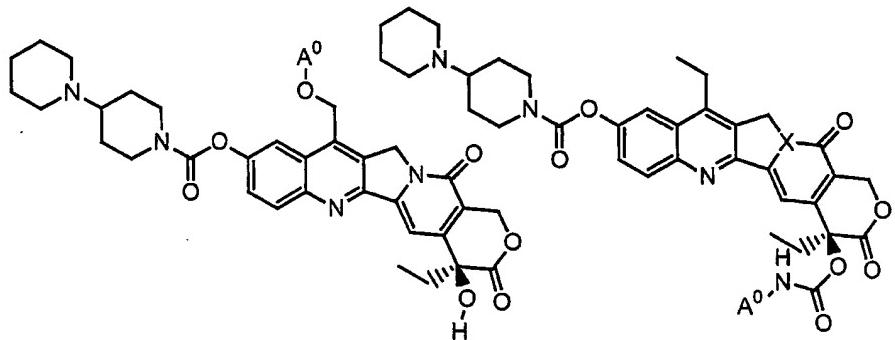
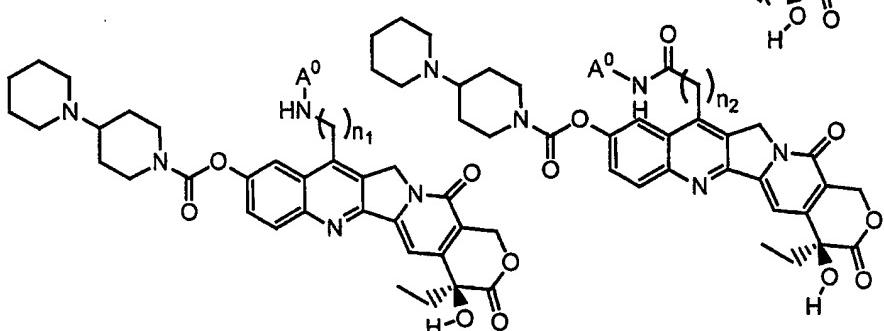
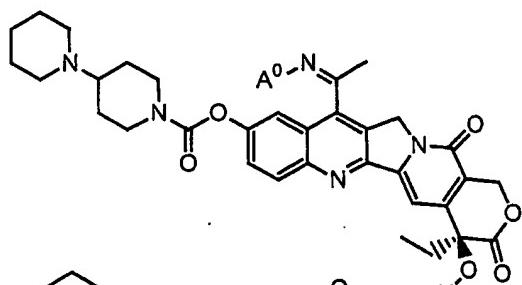
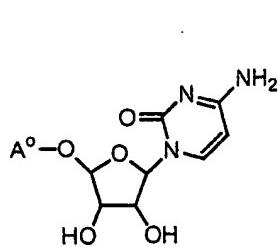
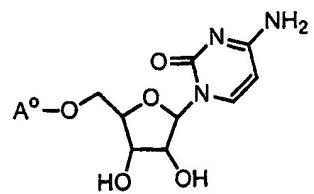
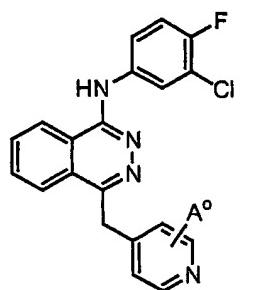
X^{61} is O or NH; and

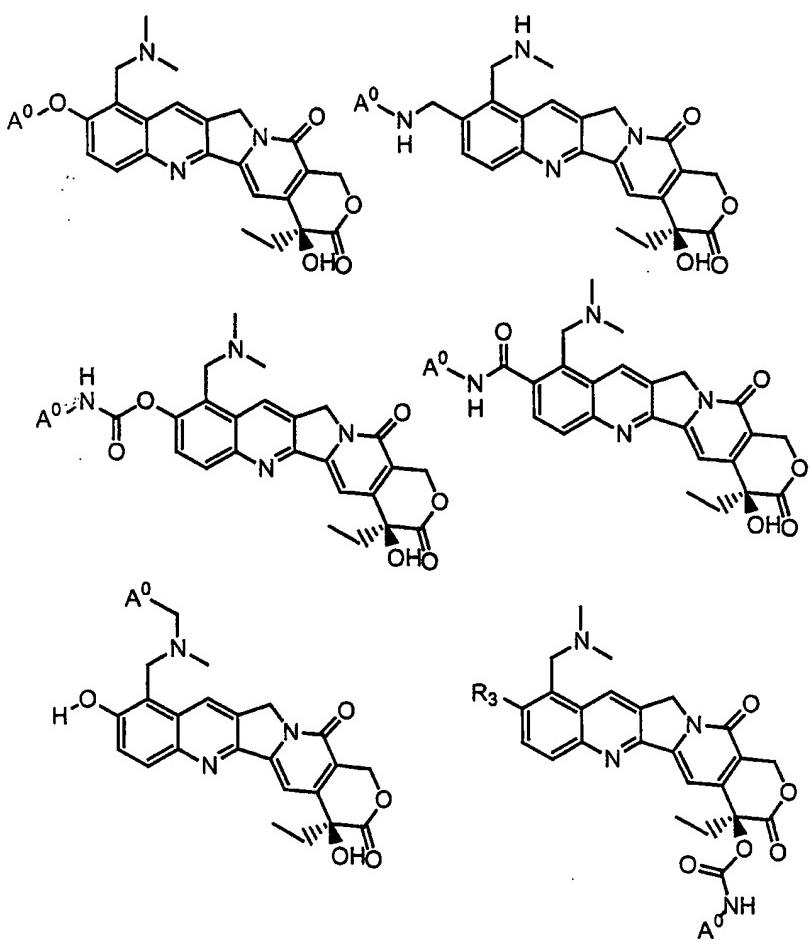
15 X^{62} , X^{63} , and X^{64} are each independently H, alkyl, aryl, or arylalkyl.

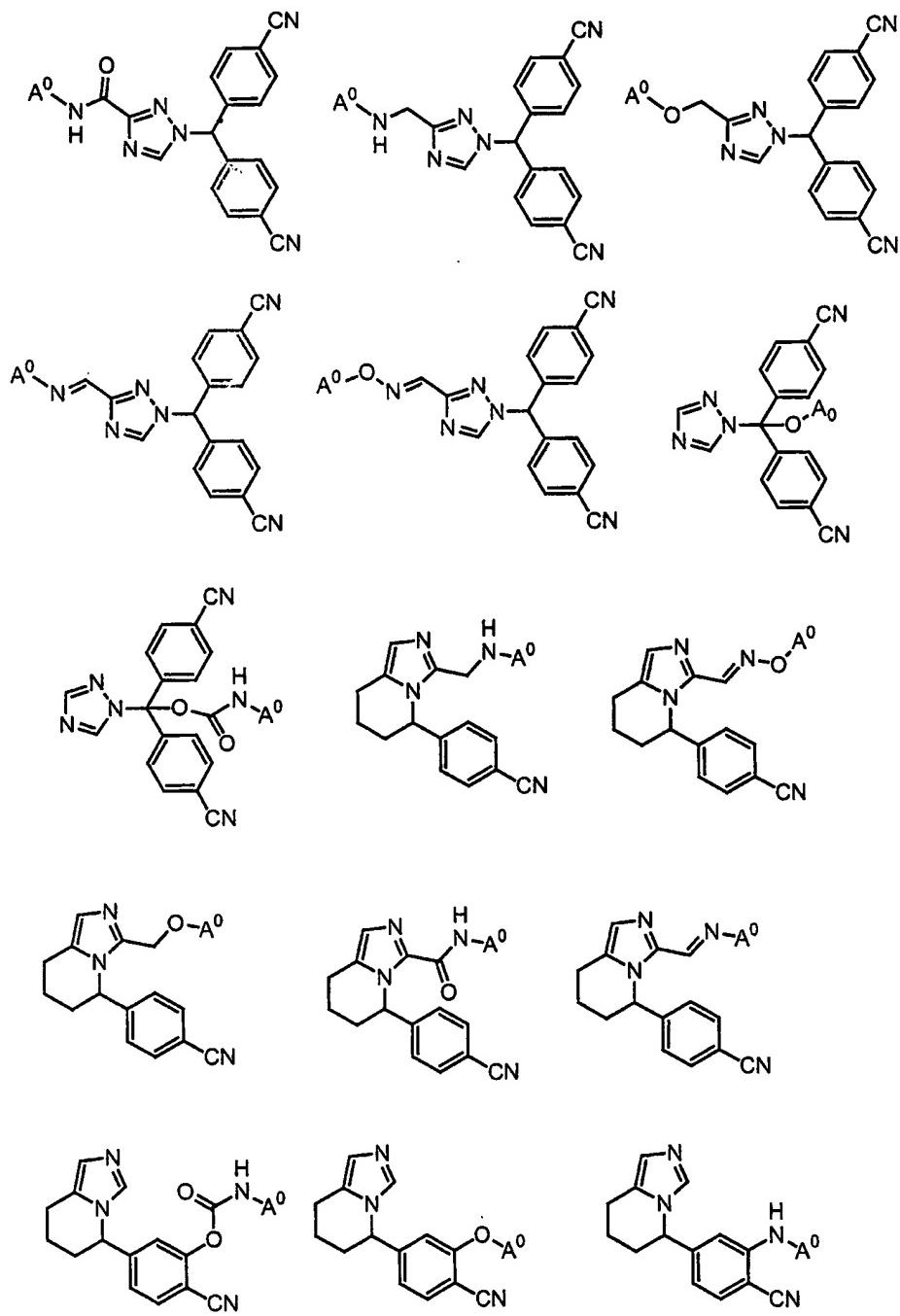
In another embodiment the invention provides a conjugate, which has any one of the following formulae:

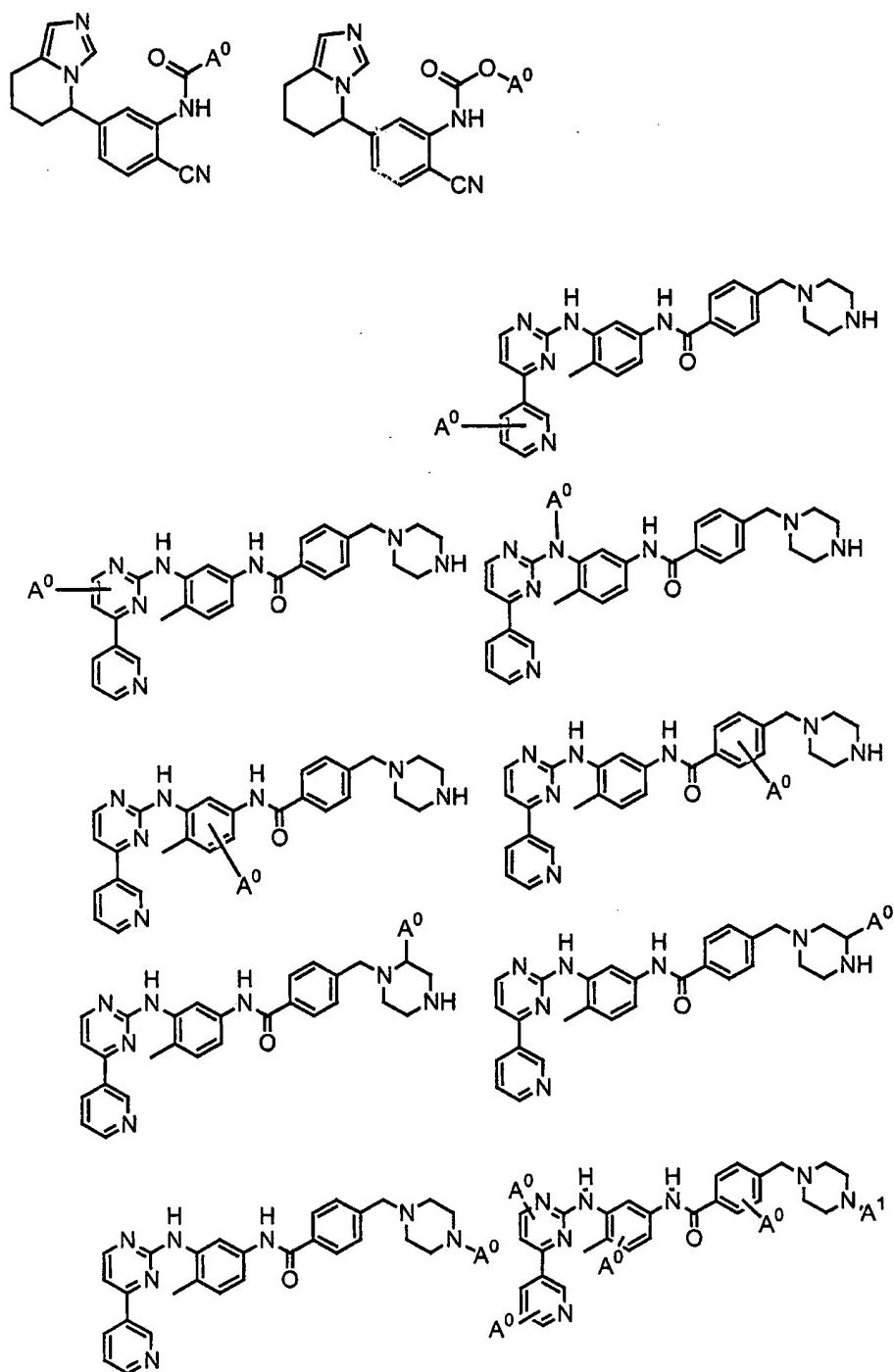


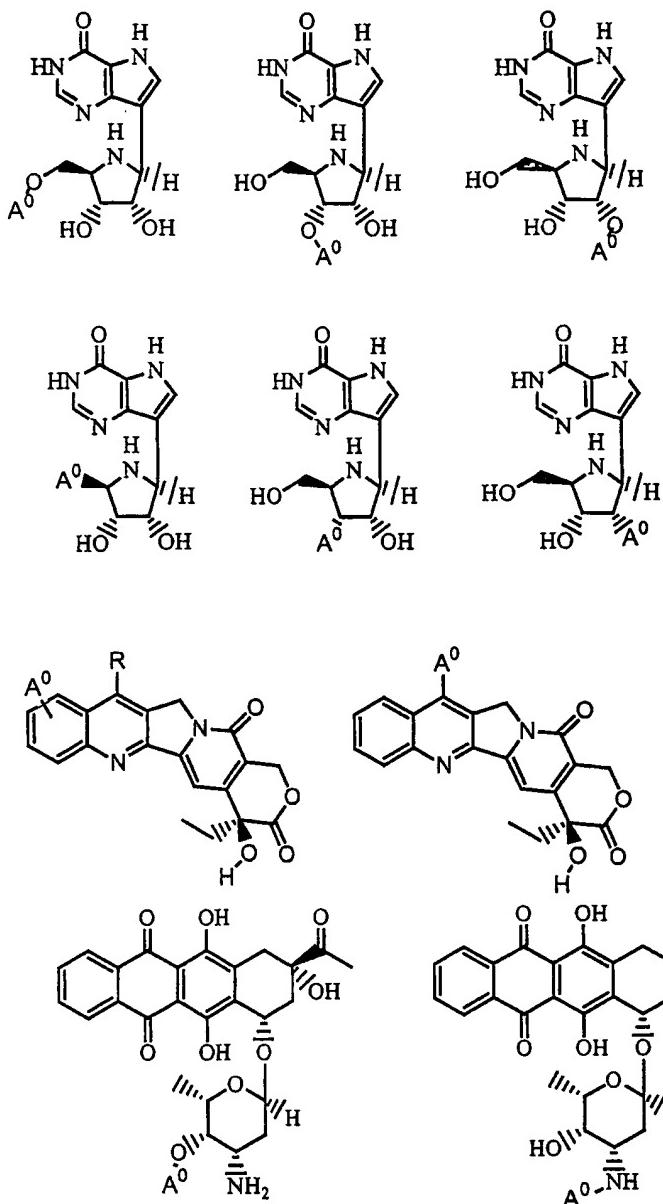


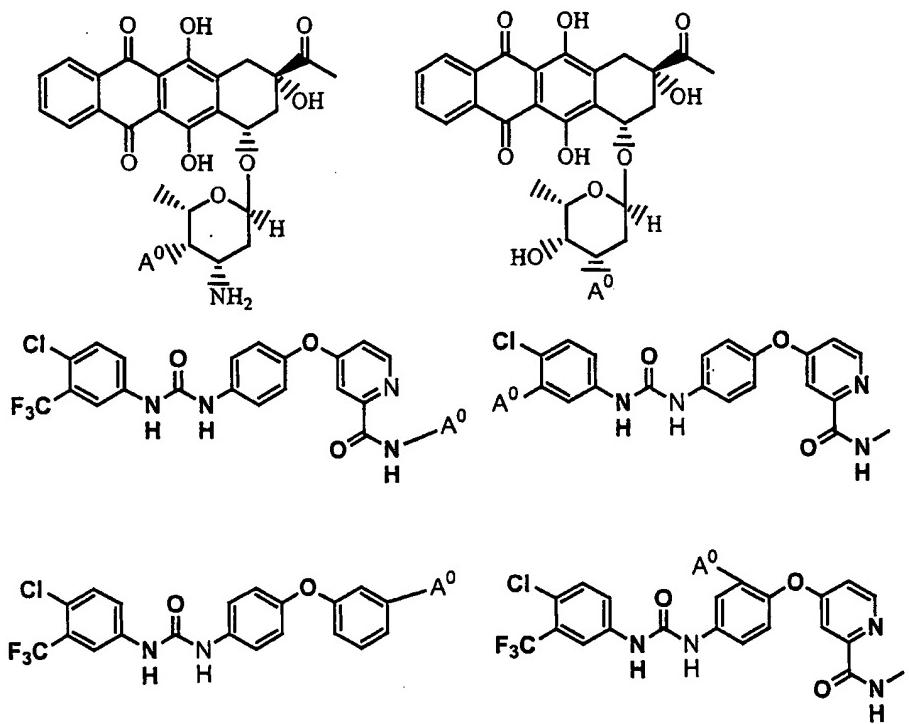


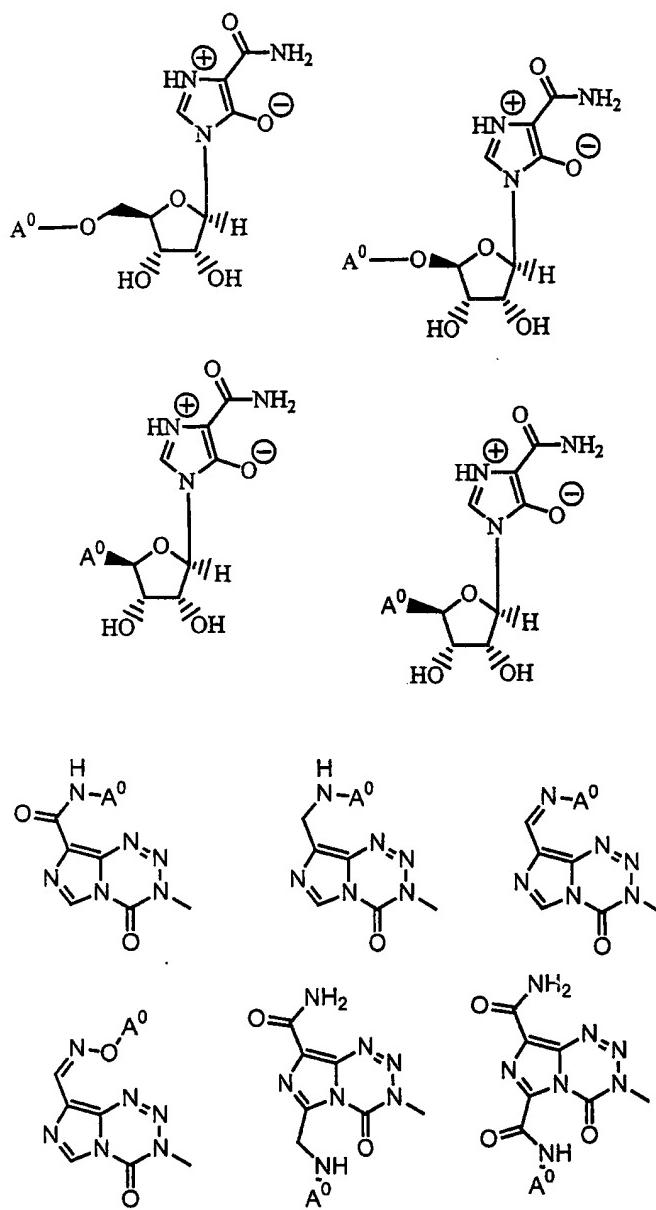


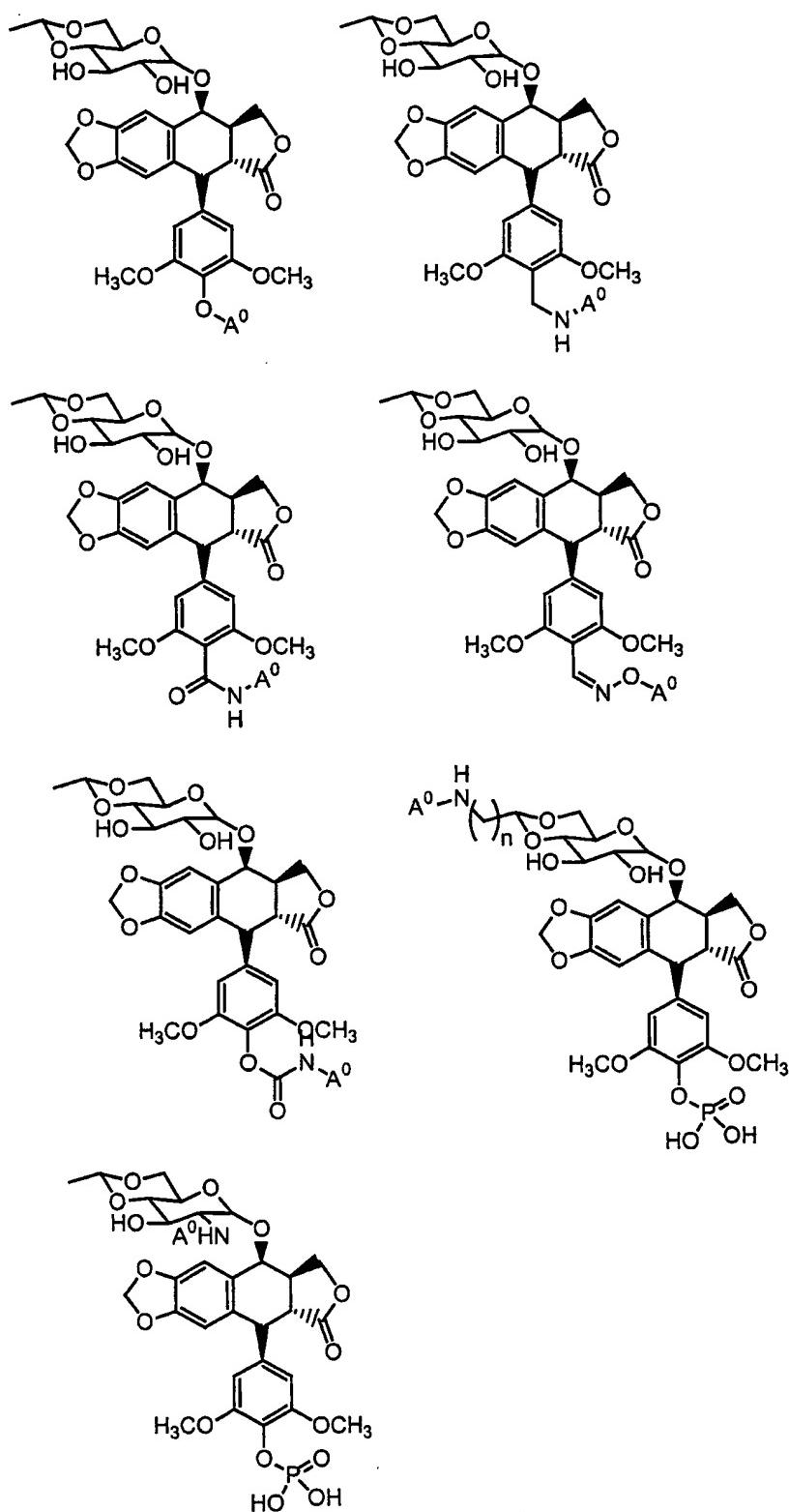


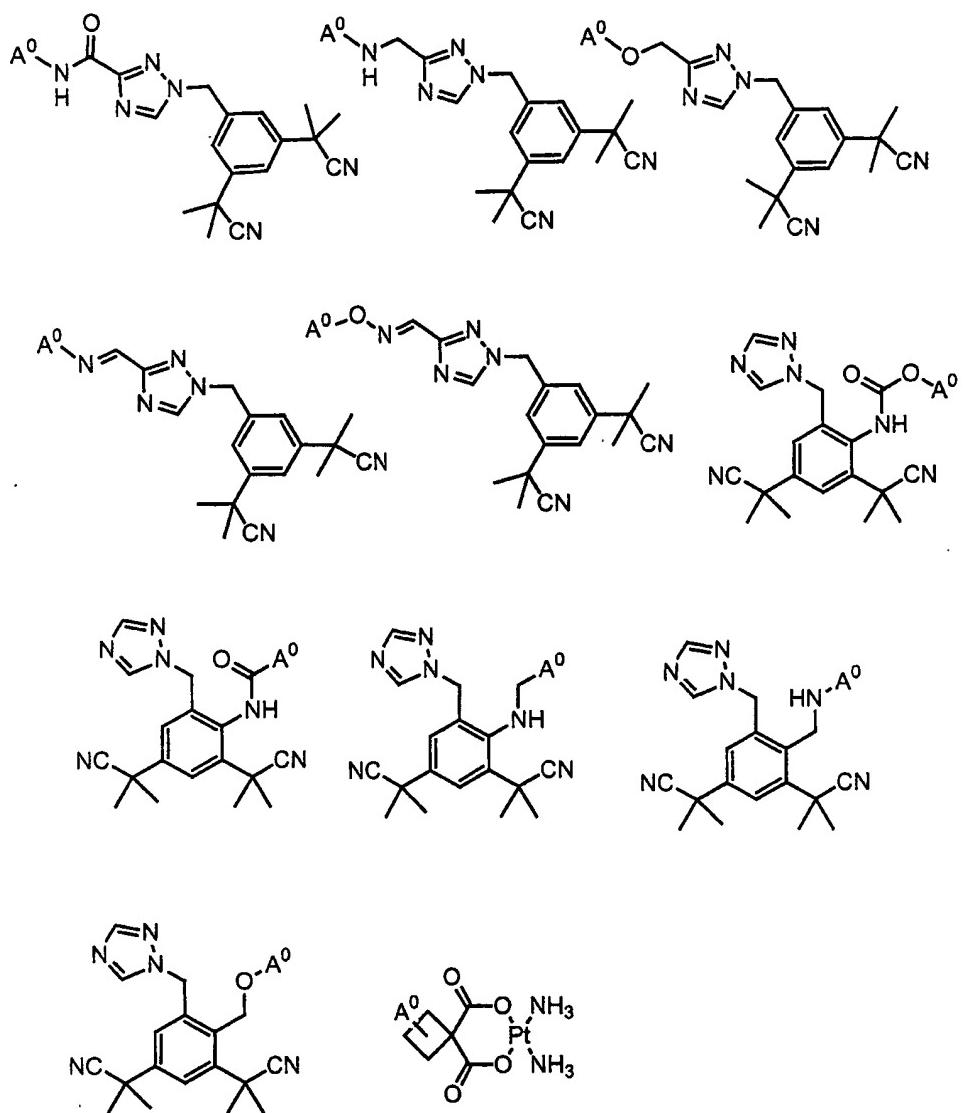


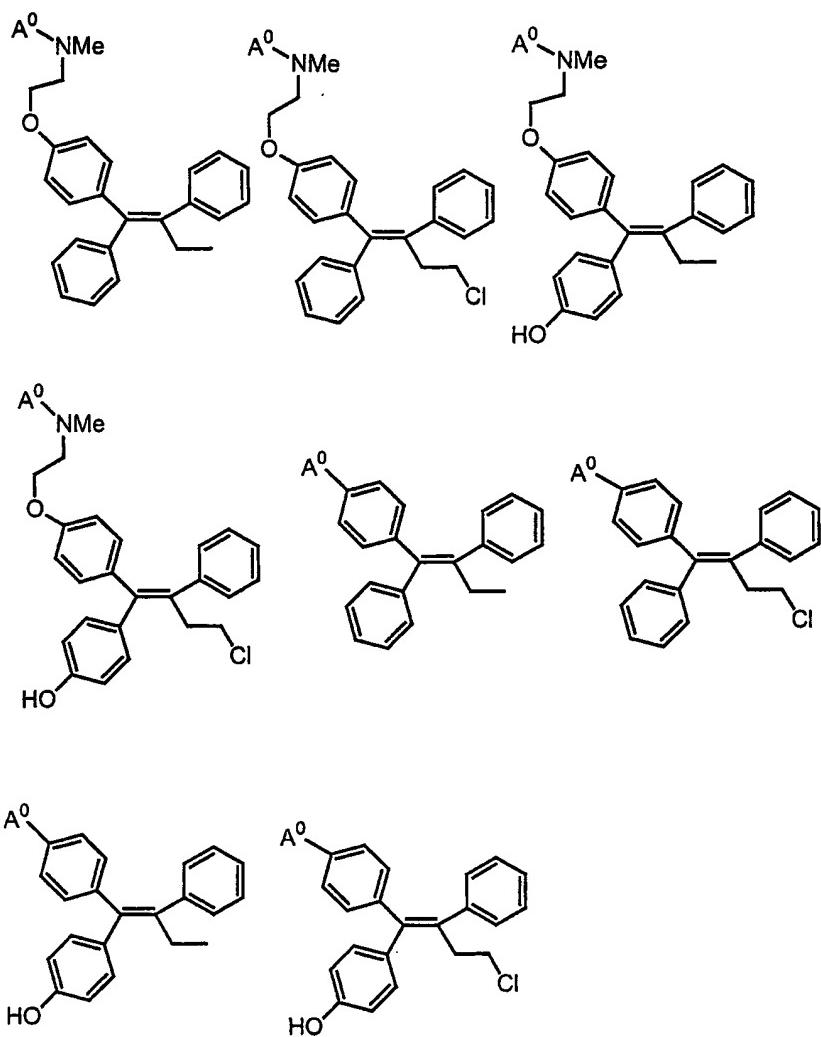


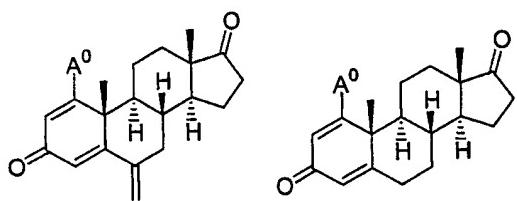
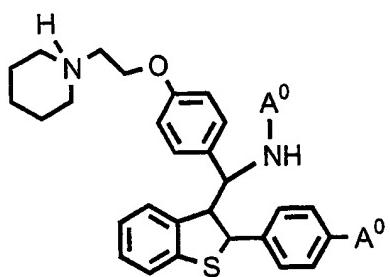
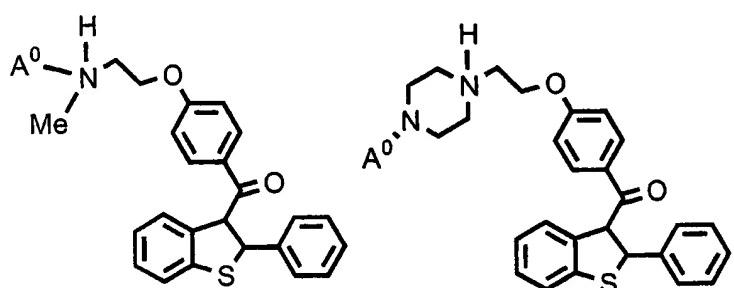
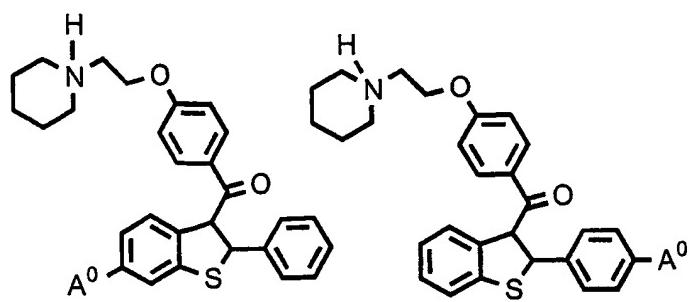


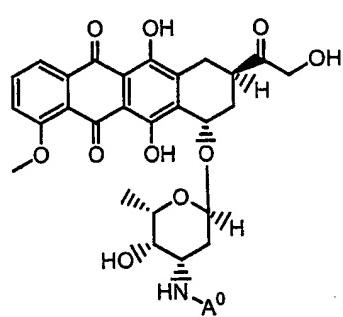
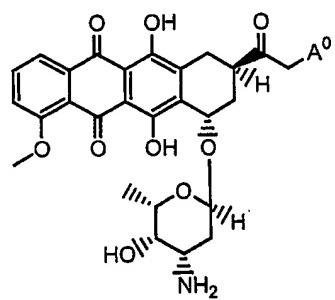
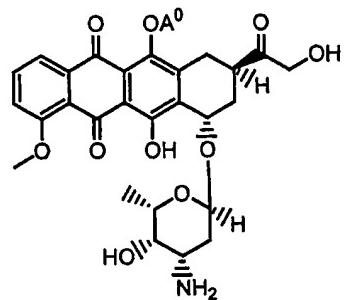
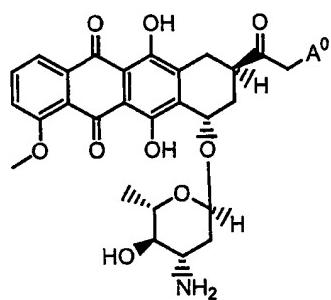
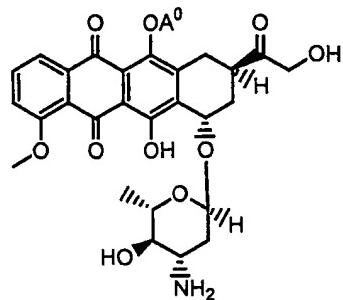
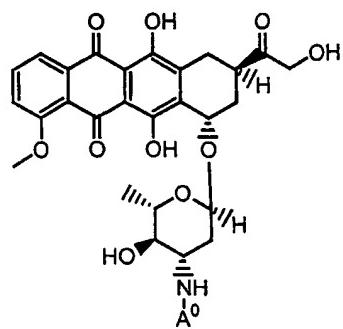


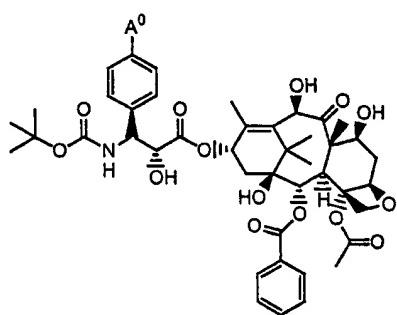
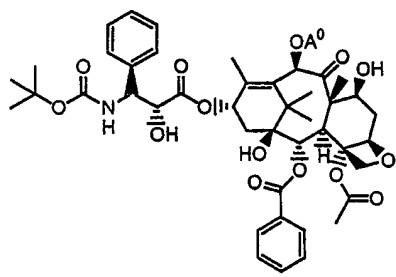
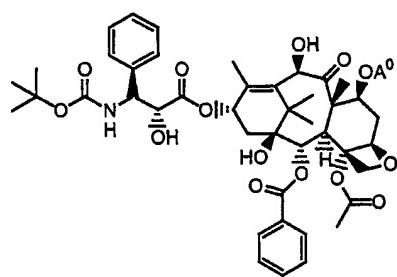
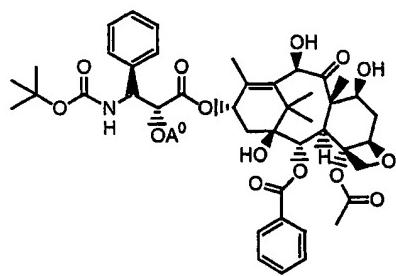
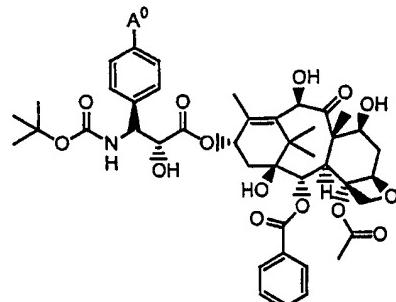
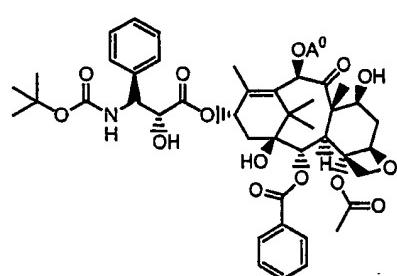
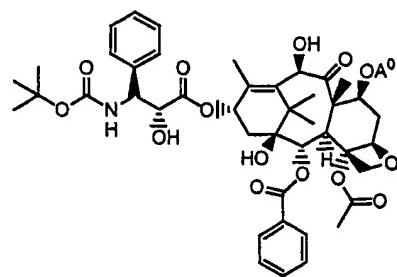
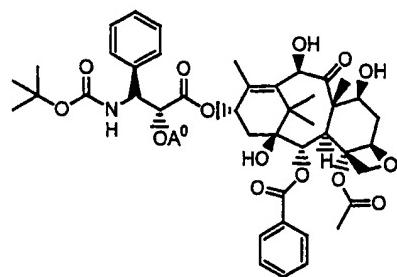


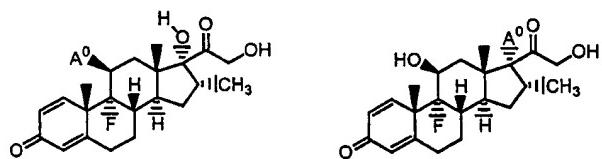
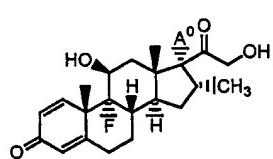
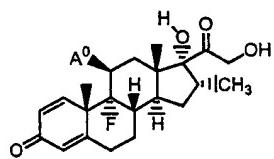
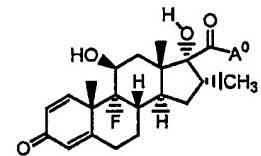
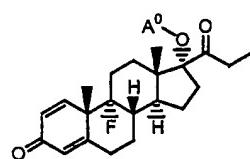
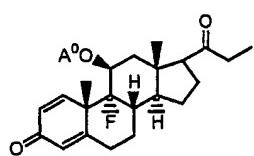
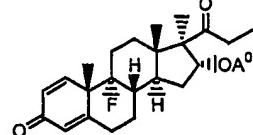
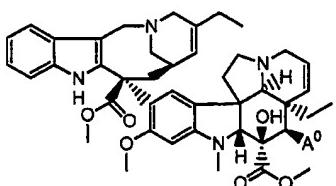
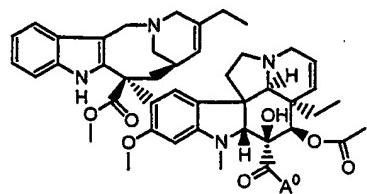
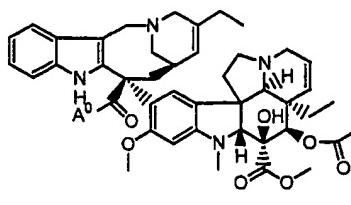


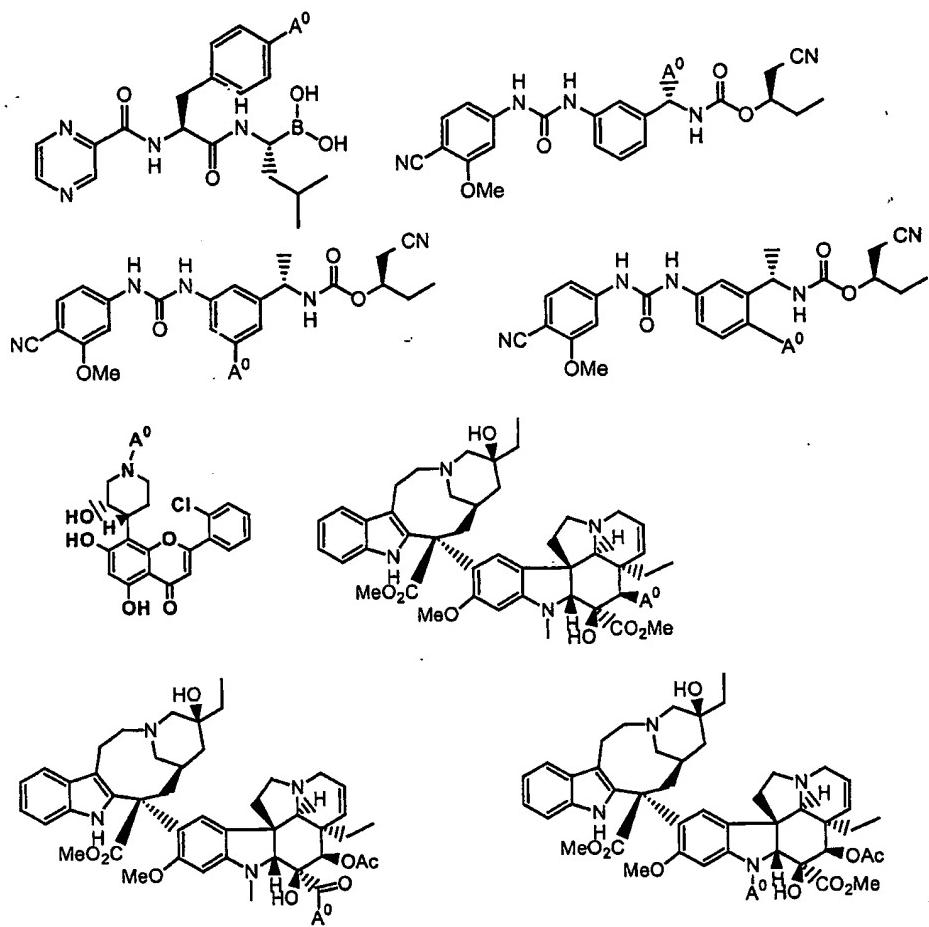


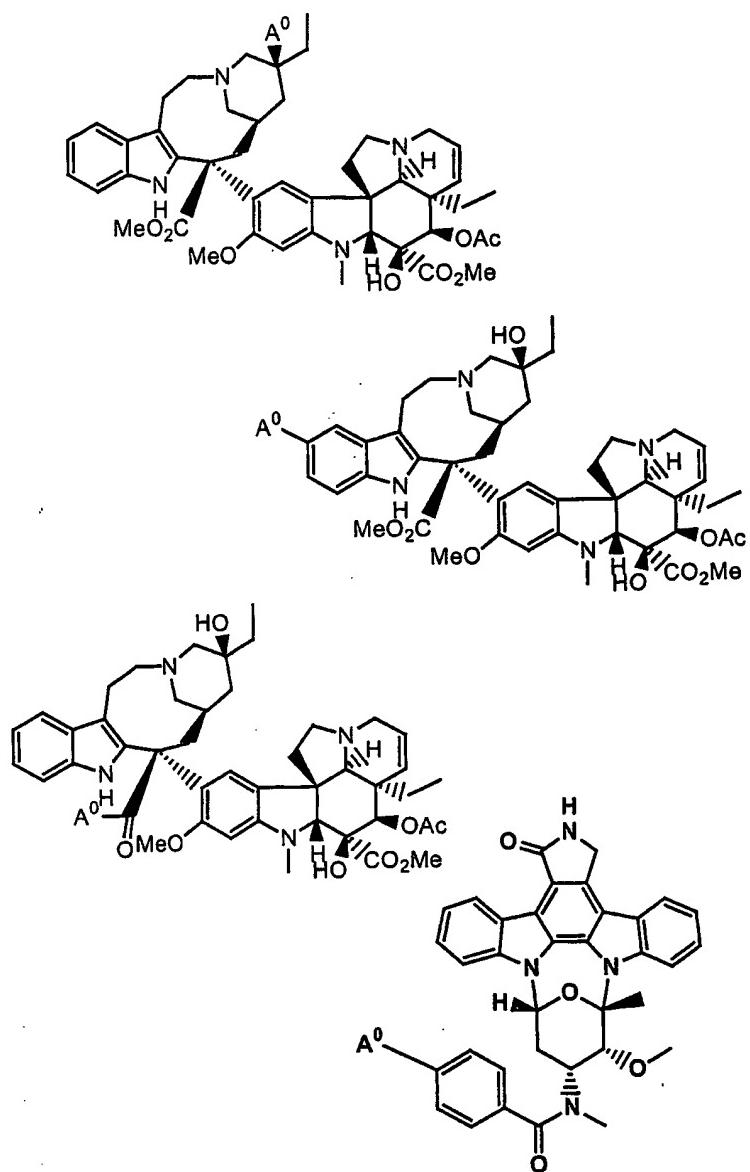


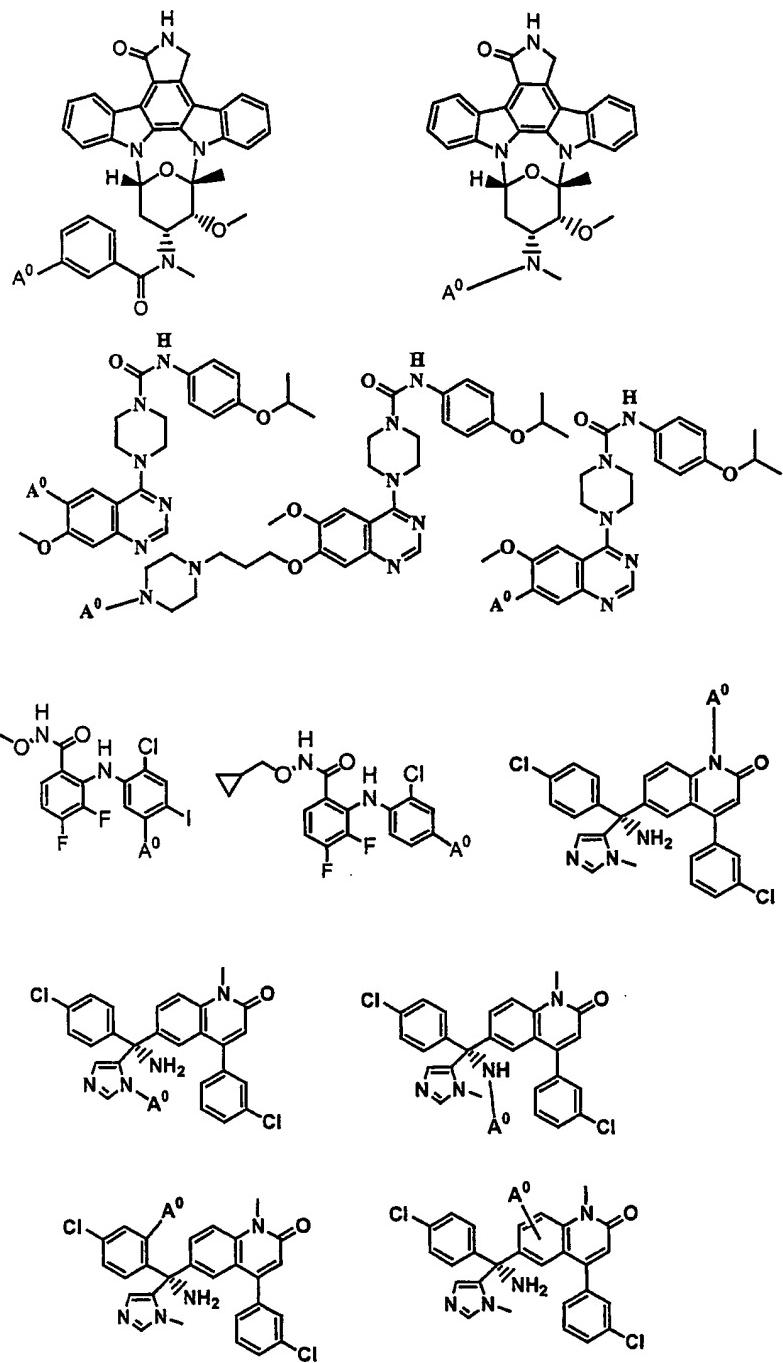


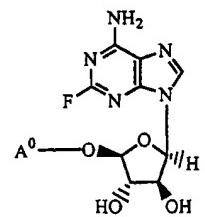
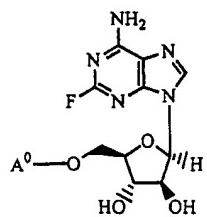
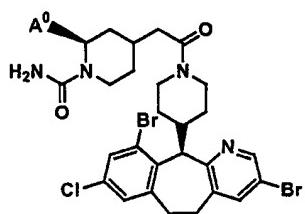
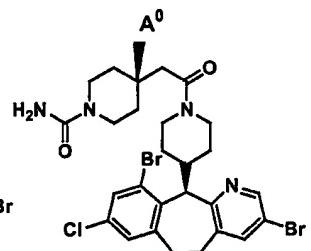
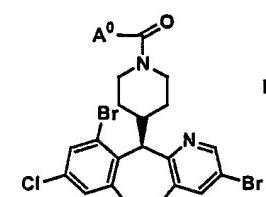
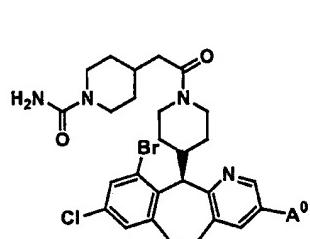
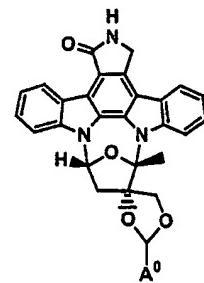
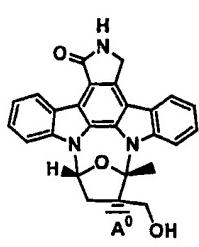
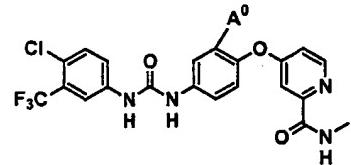
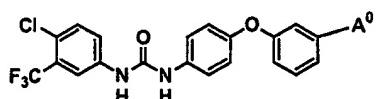
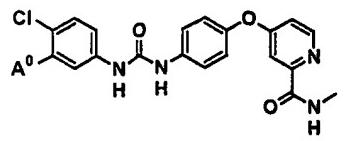
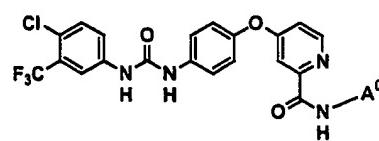


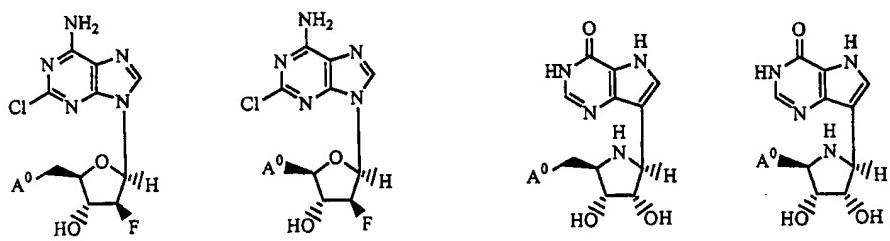
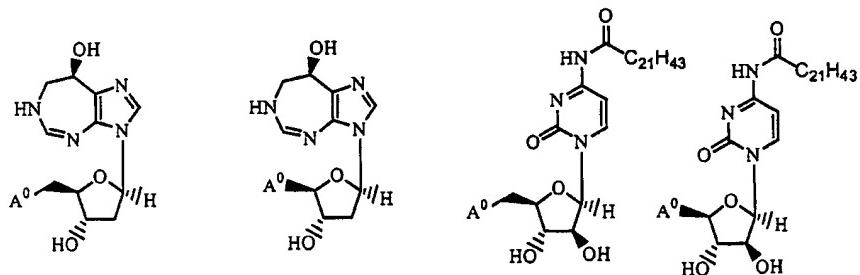
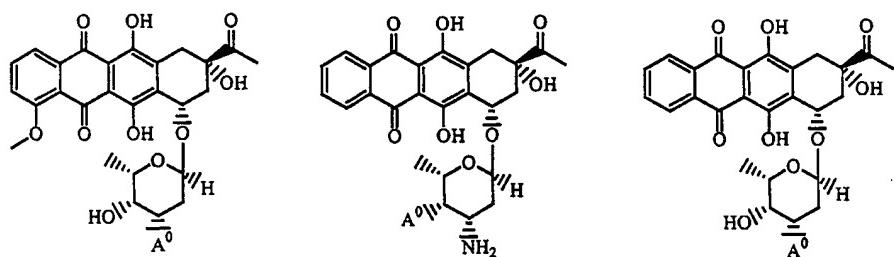
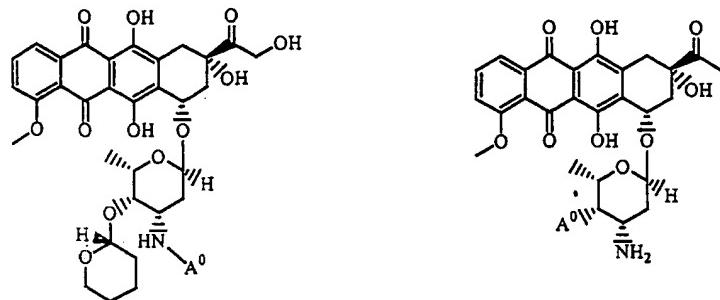


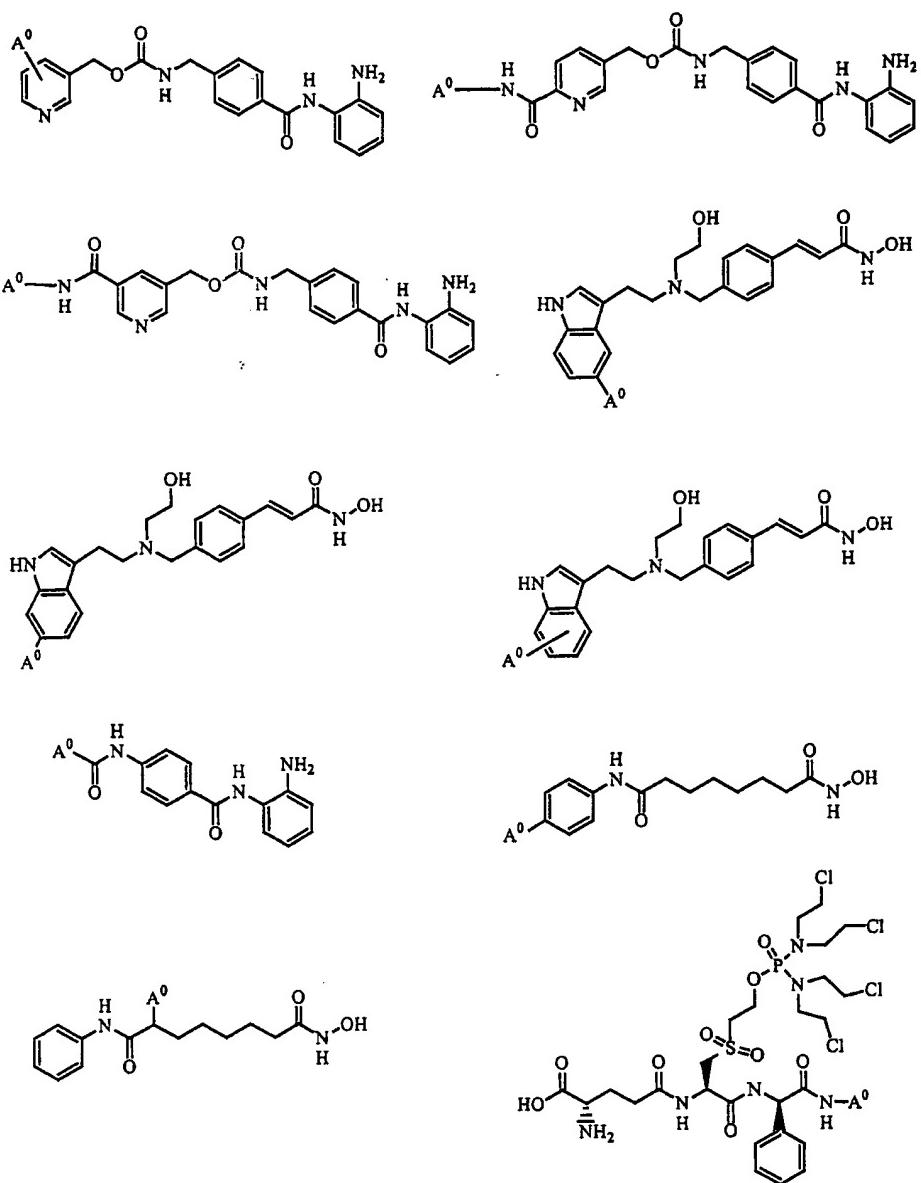


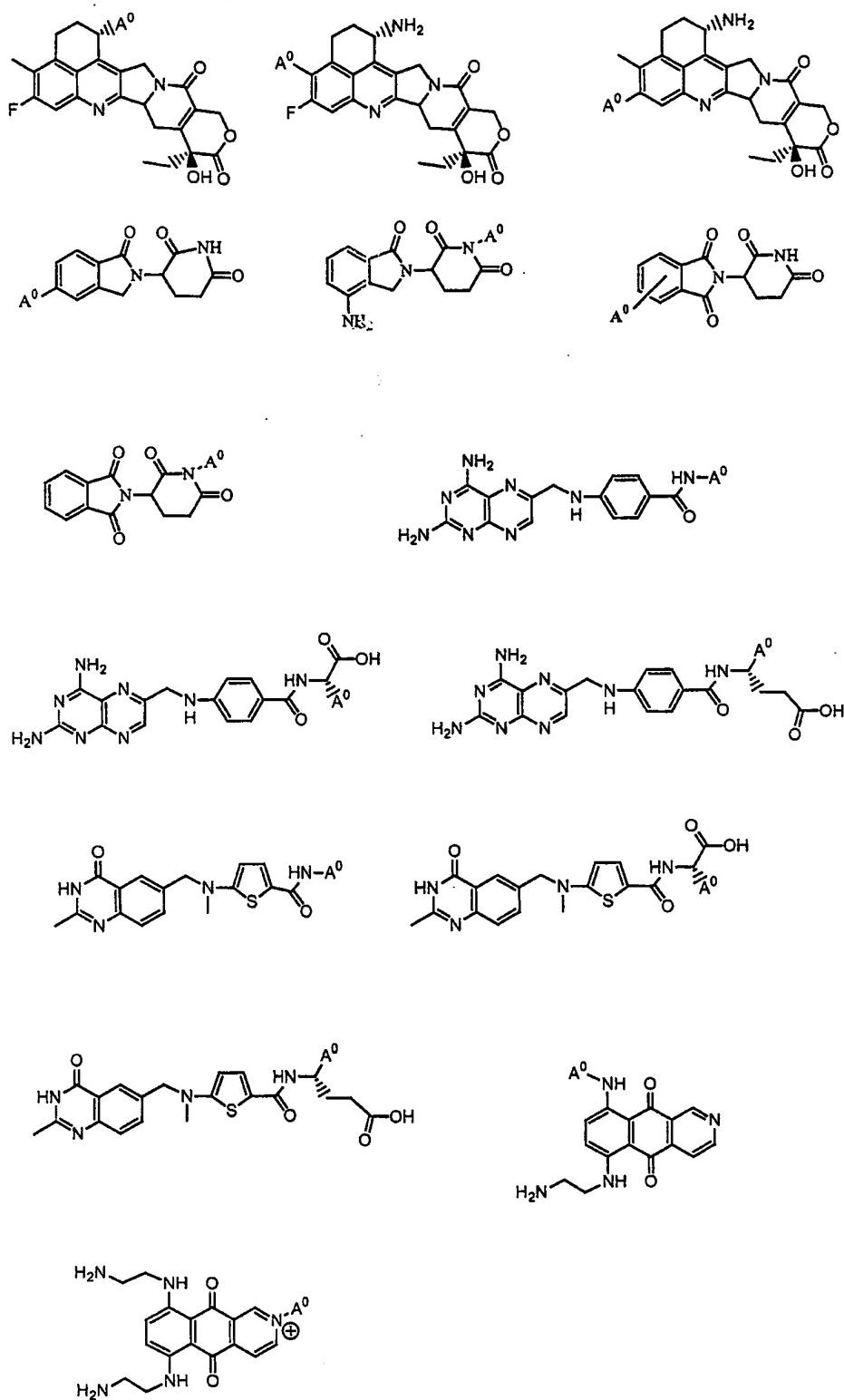


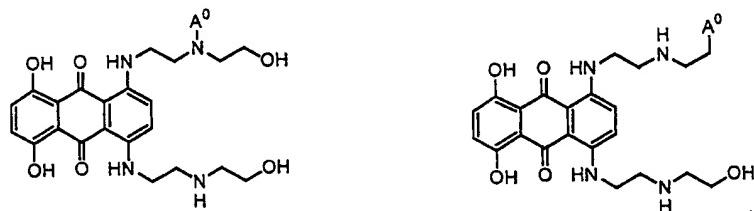
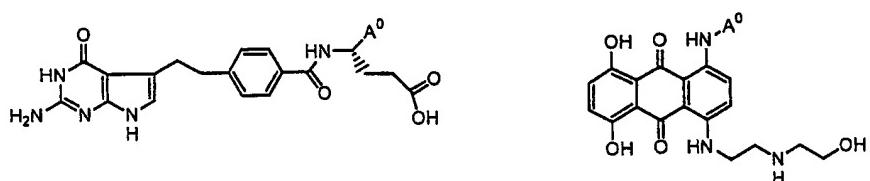
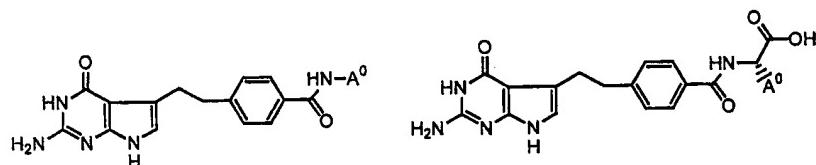
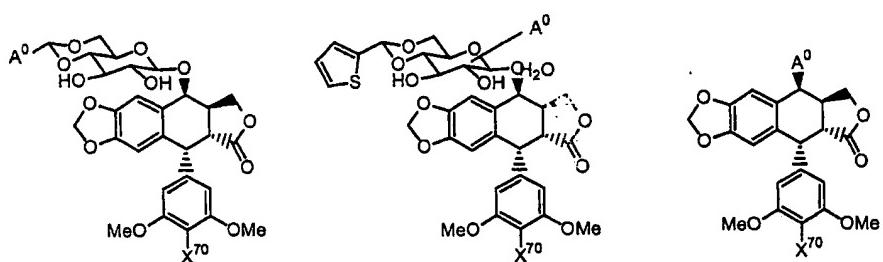
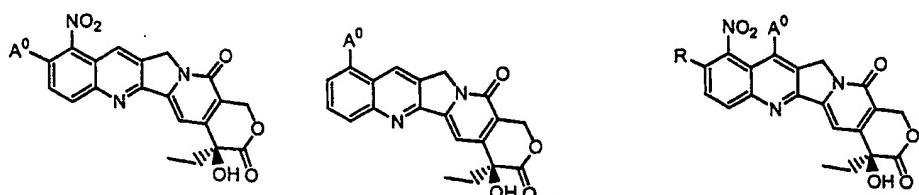


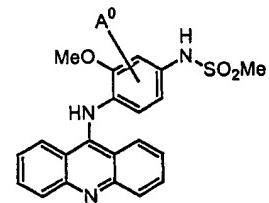
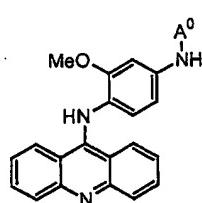
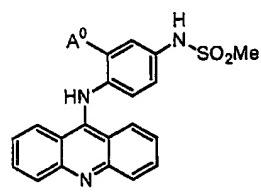
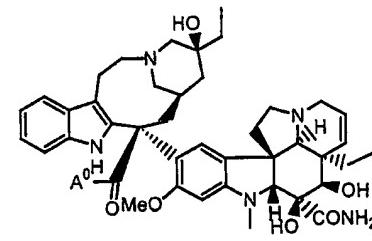
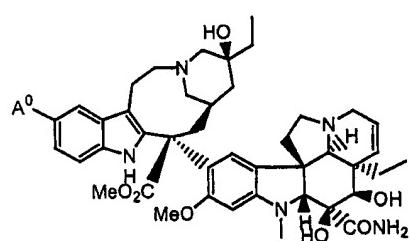
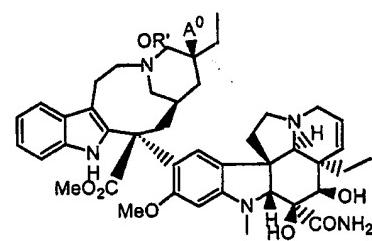
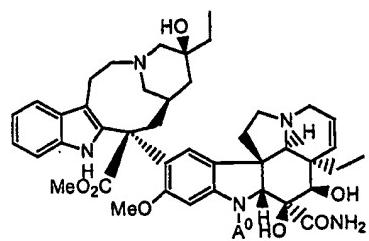
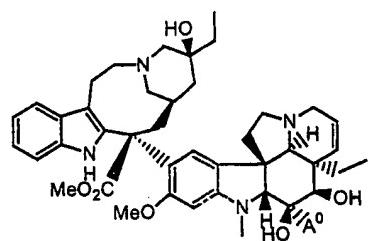
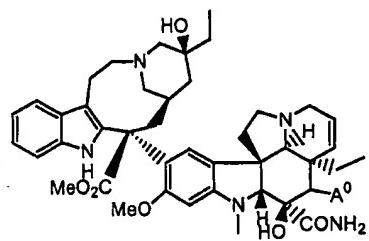


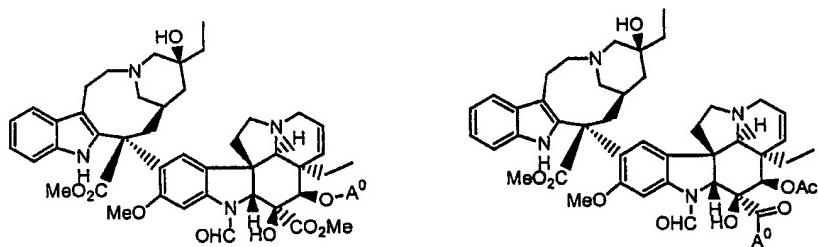
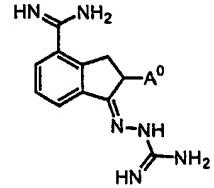
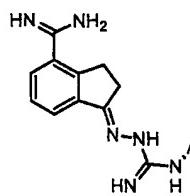
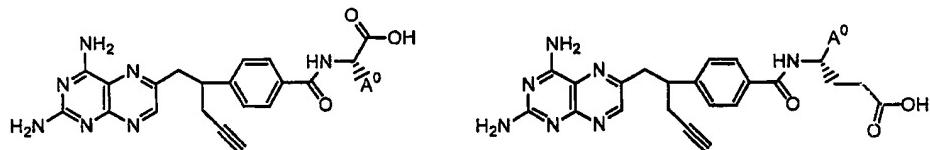
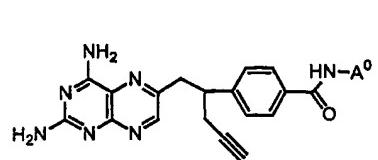
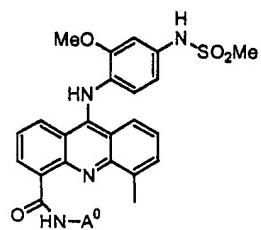


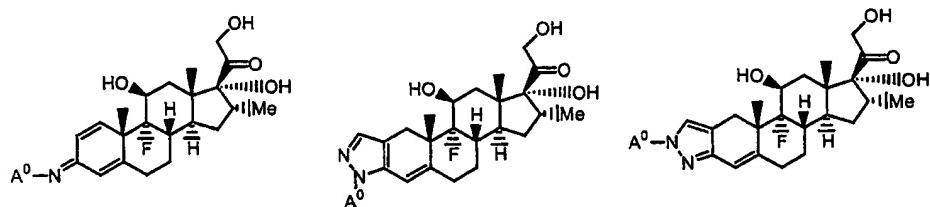
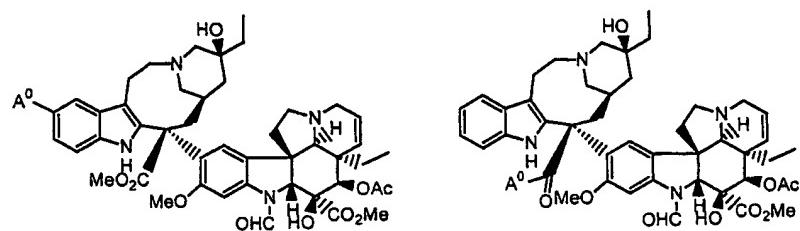
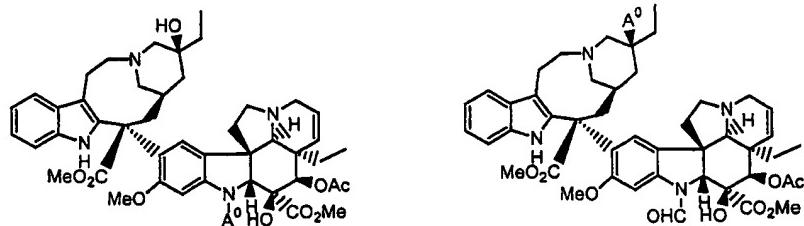


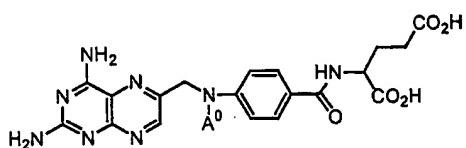
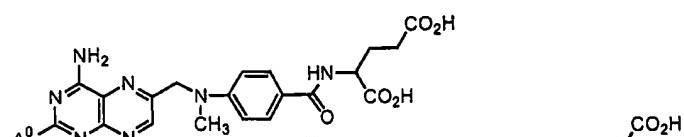
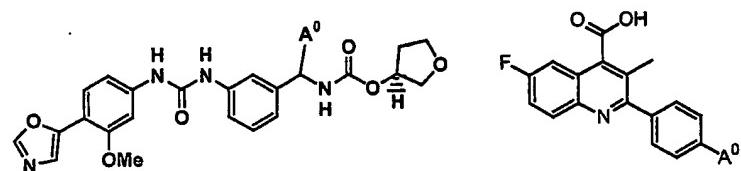
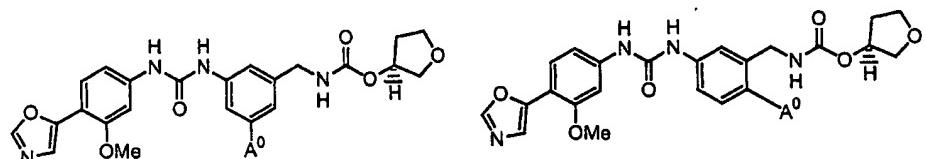
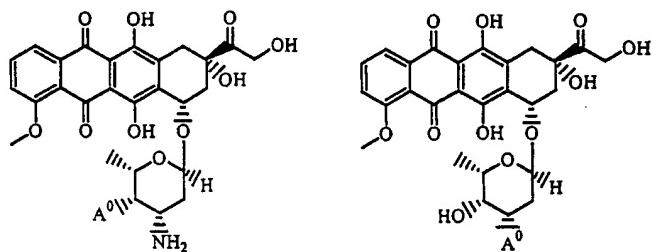


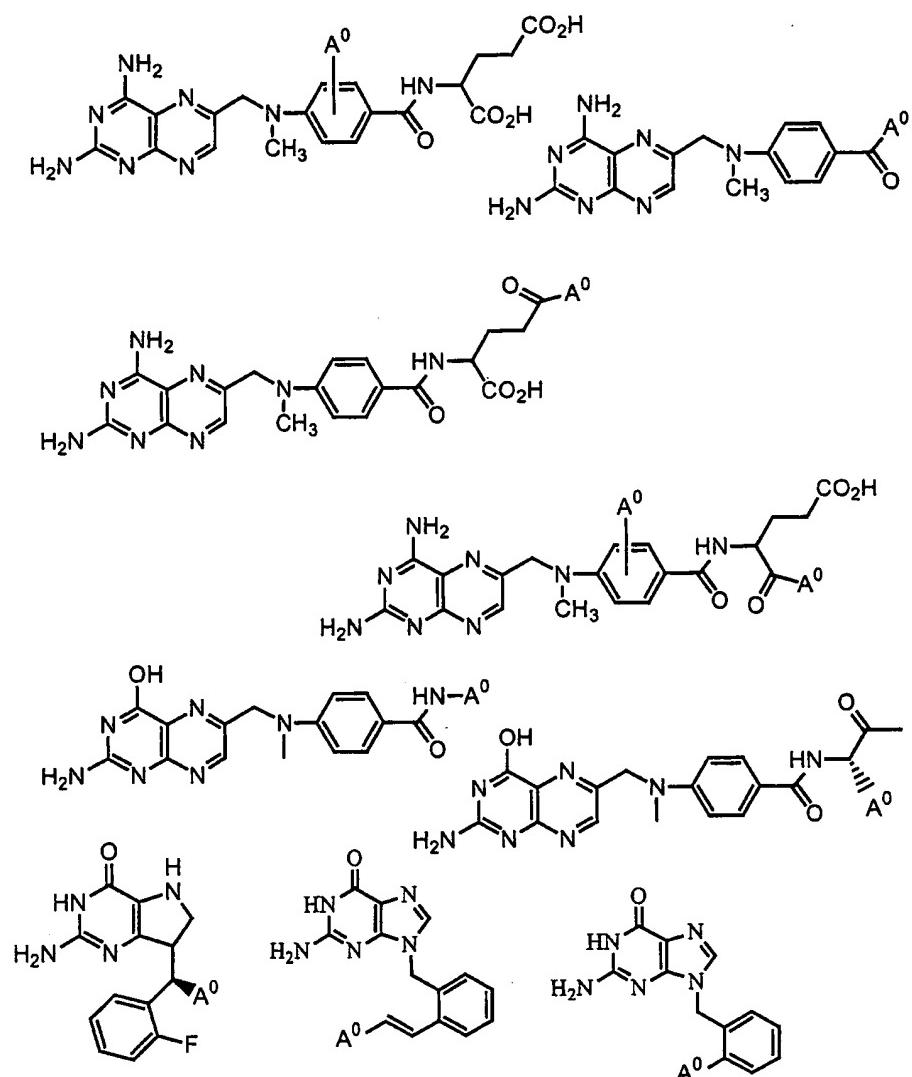


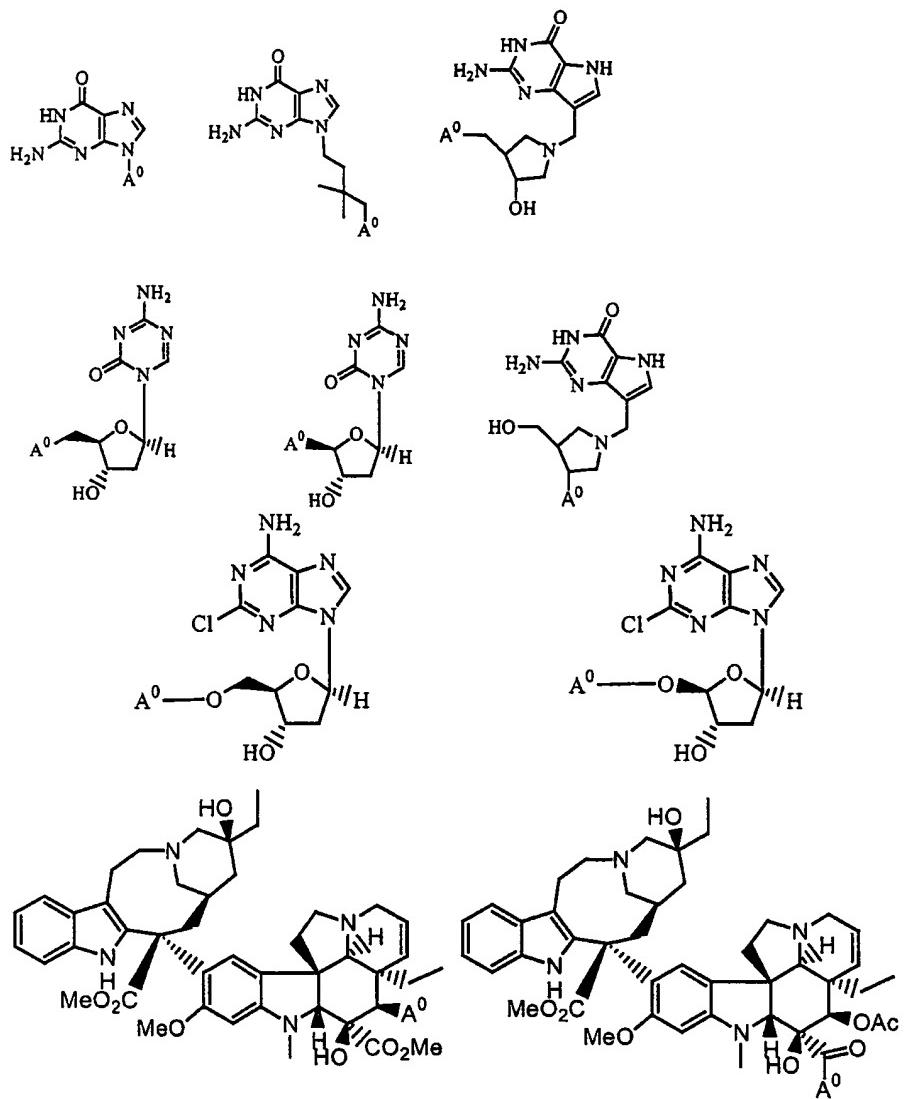


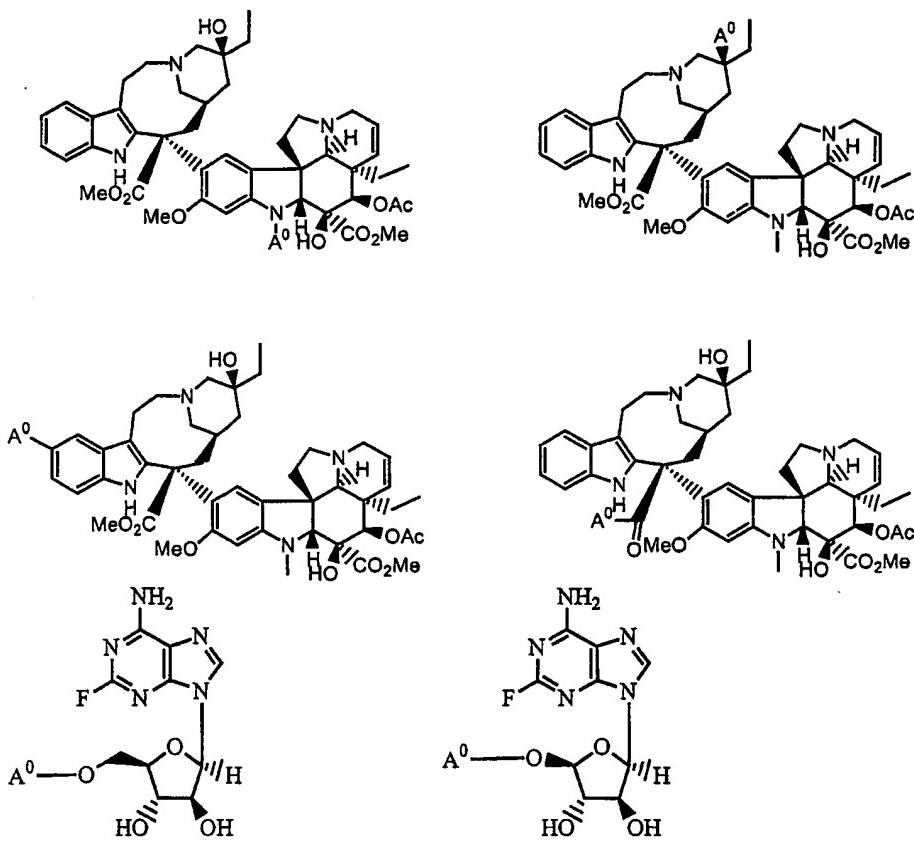








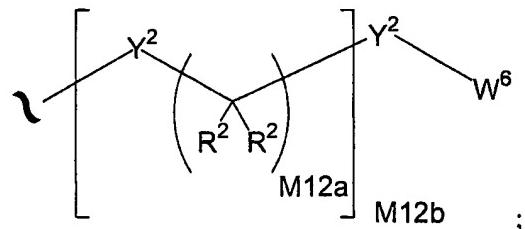




5 wherein:

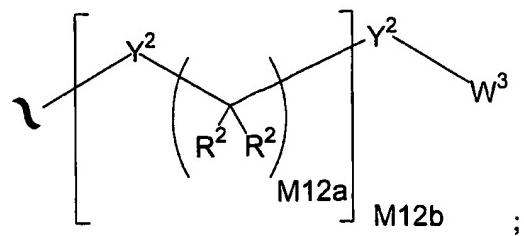
A^0 is A^1 , A^2 or W^3 with the proviso that one A^0 is A^1 ;

A^1 is:

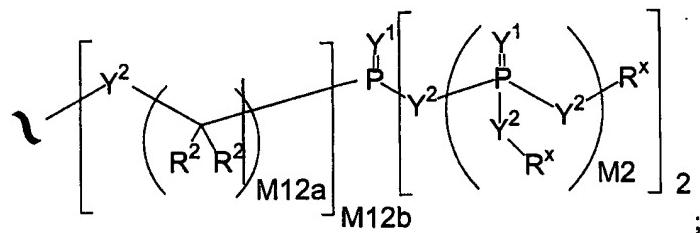


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A^2 is:



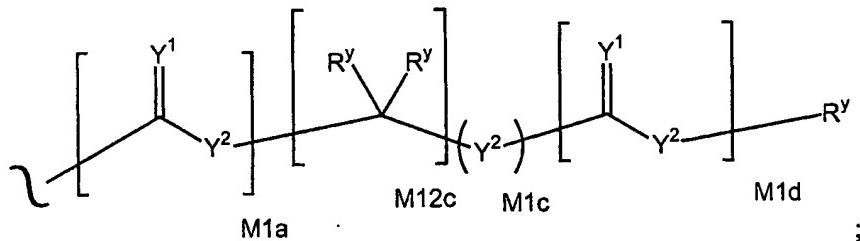
A³ is:



5 Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x))(R^x);

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x))(R^x)), -S(O)_{M2}- or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two phosphorous atoms Y² can also be C(R²)(R²);

10 R^x is independently H, R¹, R², W³, a protecting group, or the formula:



wherein:

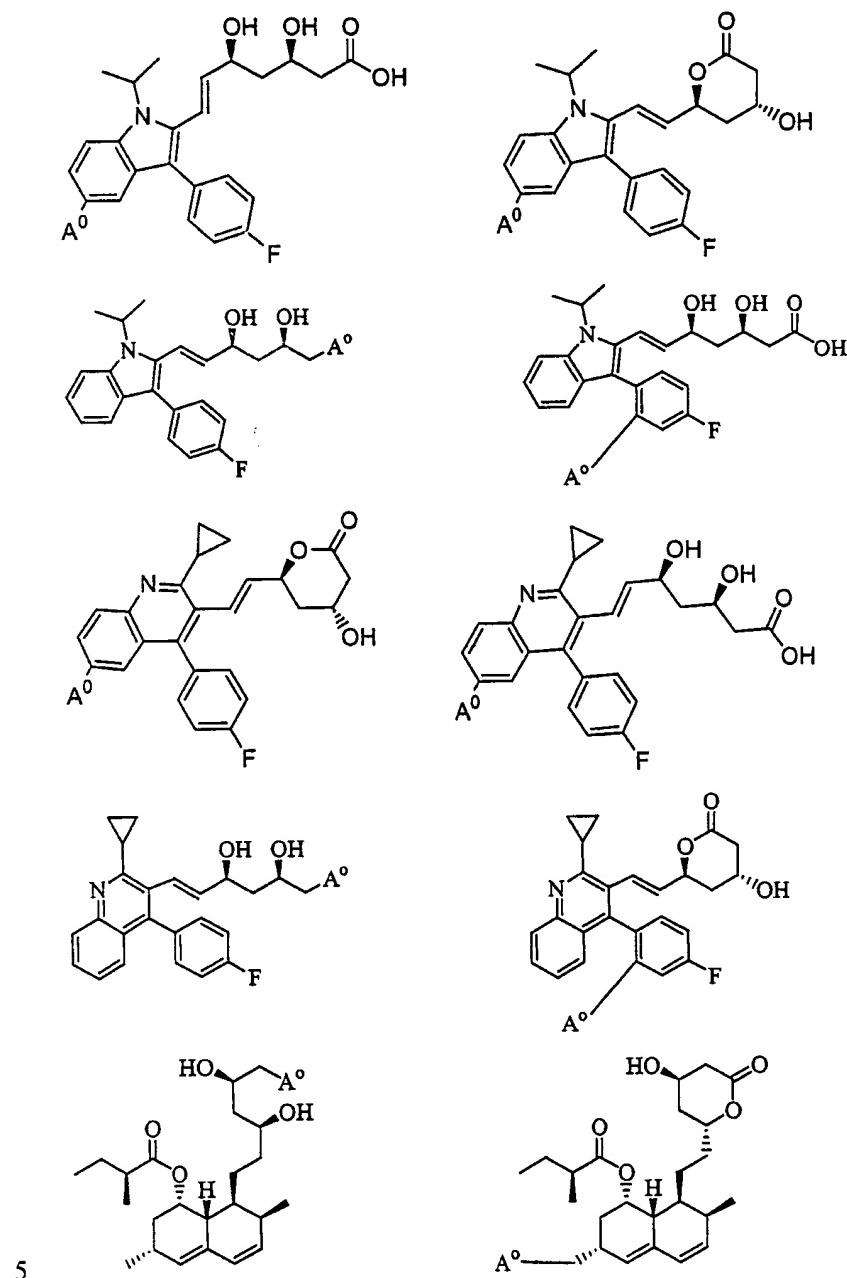
R^y is independently H, W³, R² or a protecting group;

R¹ is independently H or alkyl of 1 to 18 carbon atoms;

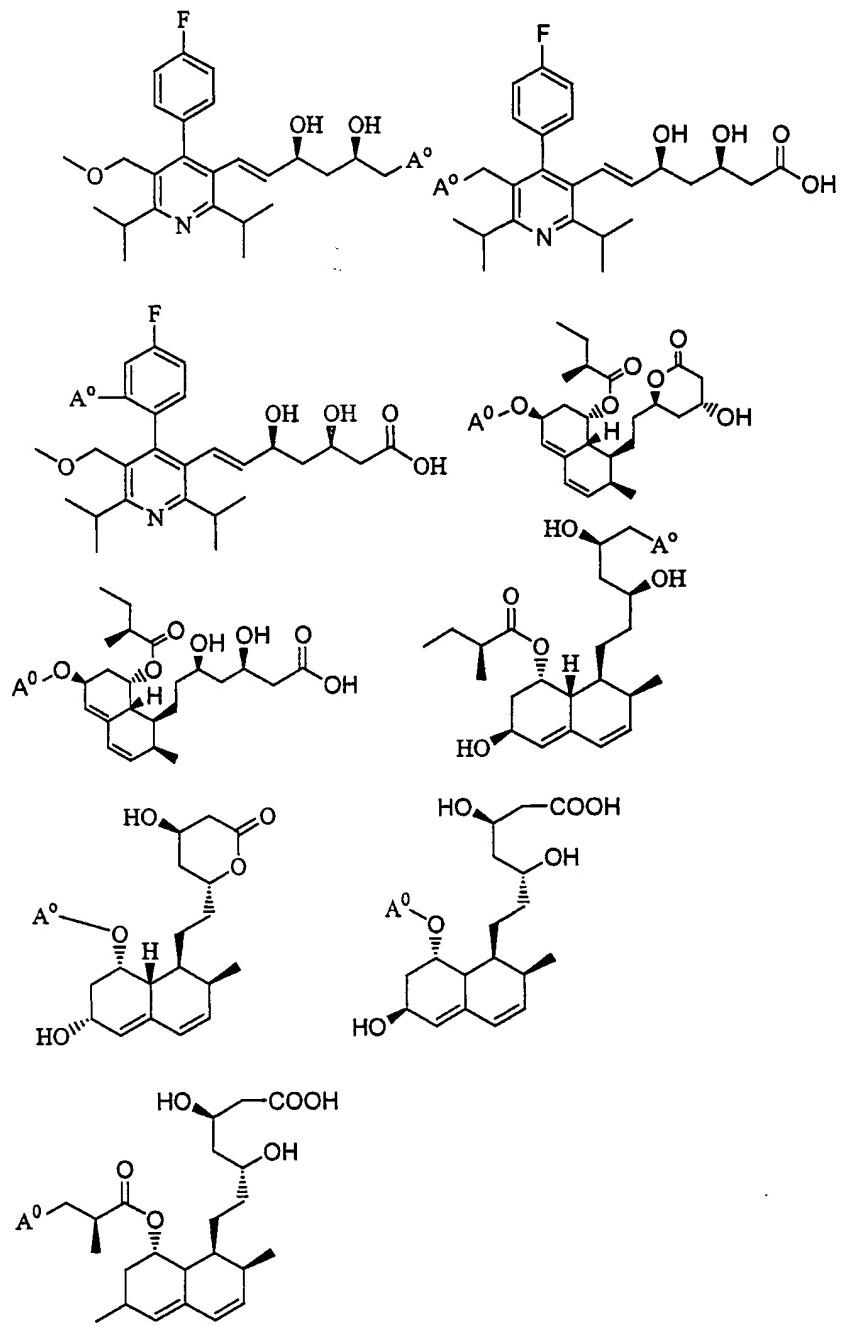
15 R² is independently H, R¹, R³ or R⁴ wherein each R⁴ is independently substituted with 0 to 3 R³ groups or taken together at a carbon atom, two R² groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R³ groups;

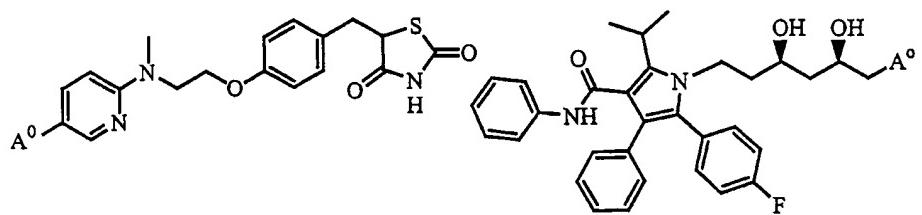
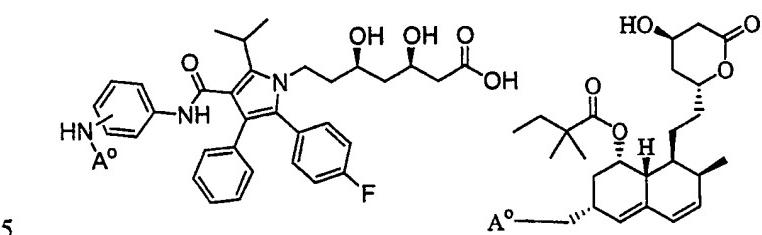
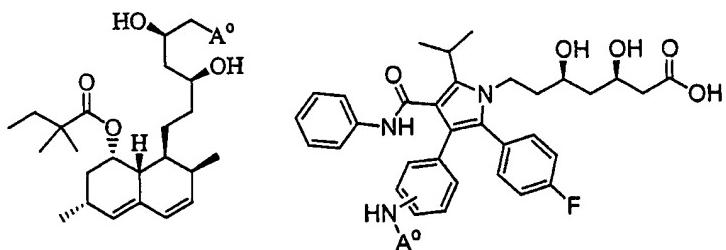
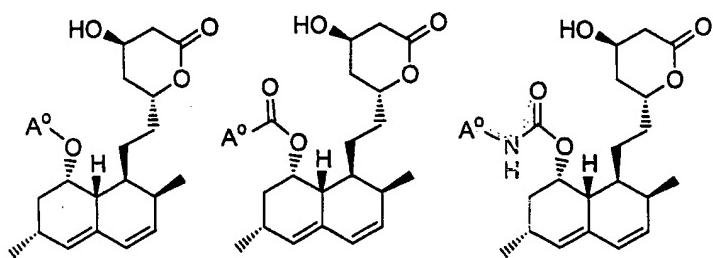
R³ is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R³ is bound to a heteroatom, then R³ is R^{3c} or R^{3d};

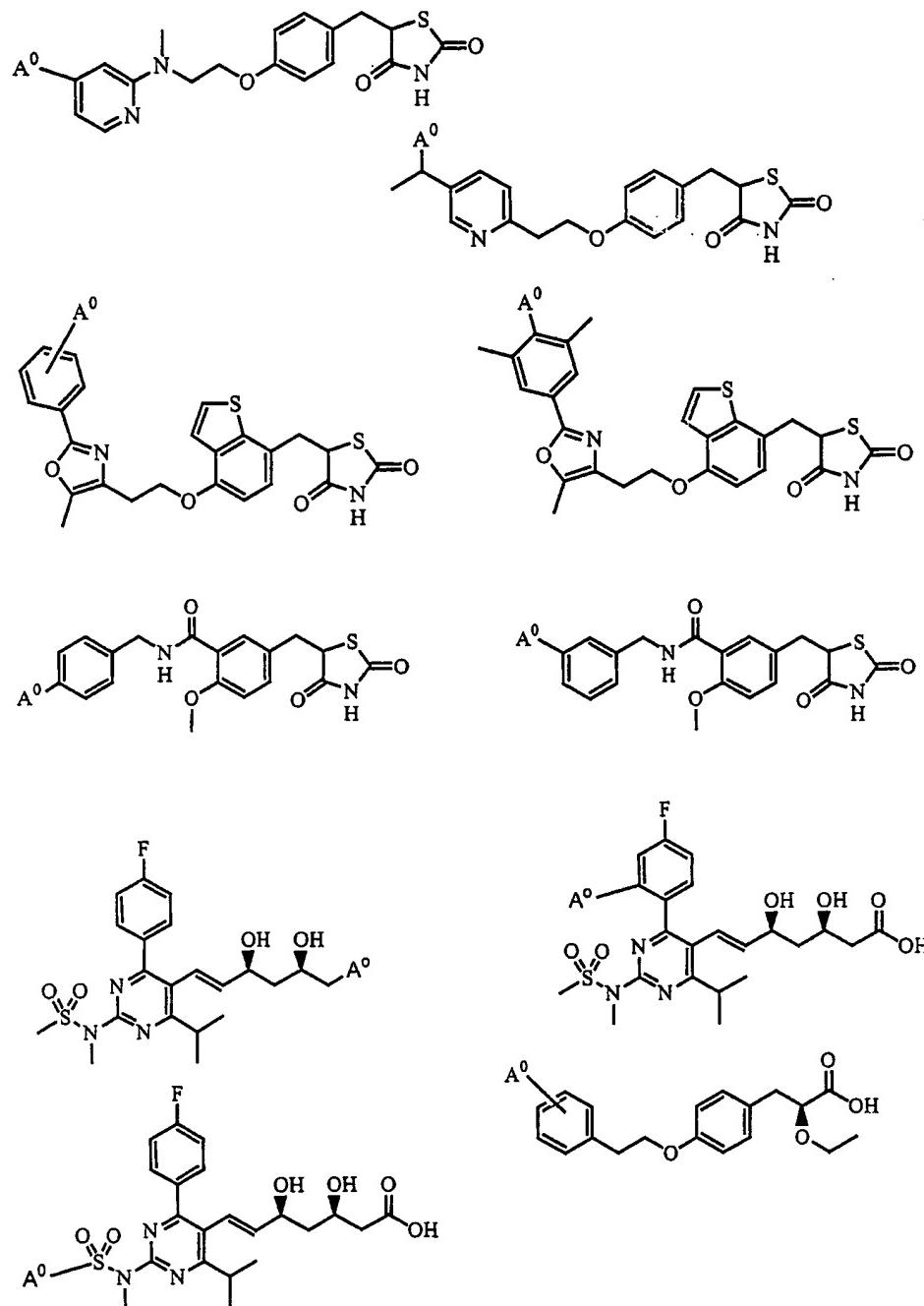
- R^{3a} is F, Cl, Br, I, -CN, N₃ or -NO₂;
- R^{3b} is Y¹;
- R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)₂R^x, -S(O)(OR^x), -S(O)₂(OR^x), -OC(Y¹)R^x, -OC(Y¹)OR^x, -OC(Y¹)(N(R^x)(R^x)), -SC(Y¹)R^x, -SC(Y¹)OR^x, -SC(Y¹)(N(R^x)(R^x)), -N(R^x)C(Y¹)R^x, -N(R^x)C(Y¹)OR^x, or -N(R^x)C(Y¹)(N(R^x)(R^x));
- R^{3d} is -C(Y¹)R^x, -C(Y¹)OR^x or -C(Y¹)(N(R^x)(R^x));
- R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;
- 10 R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;
- R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;
- W^3 is W^4 or W^5 ;
- 15 W^4 is R^5 , -C(Y¹)R⁵, -C(Y¹)W⁵, -SO₂R⁵, or -SO₂W⁵;
- W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;
- W^6 is W^3 independently substituted with 1, 2, or 3 A³ groups;
- 20 M2 is 0, 1 or 2;
- M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M1a, M1c, and M1d are independently 0 or 1;
- M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and
- X^{70} is hydroxy, methoxy, ethoxy, or propoxy.
- 25 In another embodiment the invention provides a conjugate, which has any one of the following formulae:



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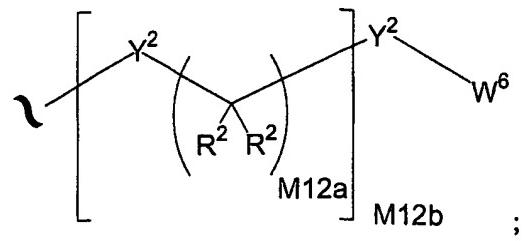




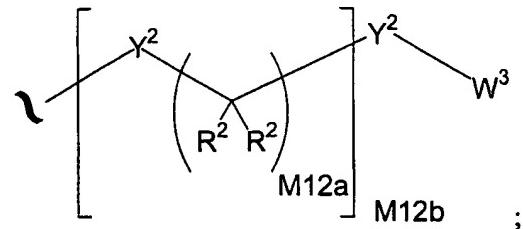
wherein:

A^0 is A^1 , A^2 or W^3 with the proviso that one A^0 is A^1 ;

10 A¹ is:

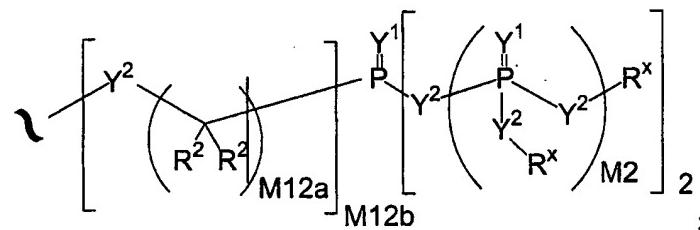


A² is:



5

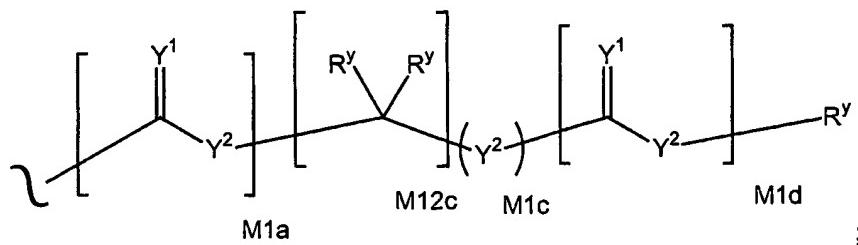
A³ is:



Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

10 Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)), -S(O)_{M2}- or -S(O)_{M2}-S(O)_{M2}-; and when Y² joins two phosphorous atoms Y² can also be C(R²)(R²);

R^x is independently H, R¹, R², W³, a protecting group, or the formula:

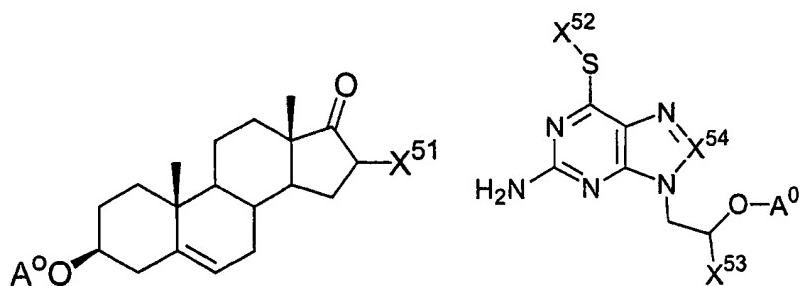


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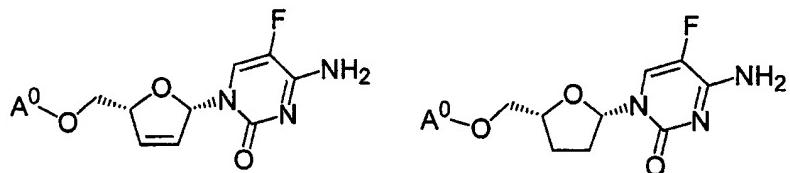
wherein:

R^y is independently H, W³, R² or a protecting group;

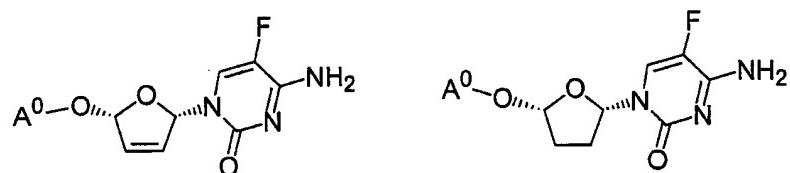
- R¹ is independently H or alkyl of 1 to 18 carbon atoms;
- R² is independently H, R¹, R³ or R⁴ wherein each R⁴ is independently substituted with 0 to 3 R³ groups or taken together at a carbon atom, two R² groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R³ groups;
- 5 R³ is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R³ is bound to a heteroatom, then R³ is R^{3c} or R^{3d};
- R^{3a} is F, Cl, Br, I, -CN, N₃ or -NO₂;
- R^{3b} is Y¹;
- 10 R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)₂R^x, -S(O)(OR^x), -S(O)₂(OR^x), -OC(Y¹)R^x, -OC(Y¹)OR^x, -OC(Y¹)(N(R^x)(R^x)), -SC(Y¹)R^x, -SC(Y¹)OR^x, -SC(Y¹)(N(R^x)(R^x)), -N(R^x)C(Y¹)R^x, -N(R^x)C(Y¹)OR^x, or -N(R^x)C(Y¹)(N(R^x)(R^x));
- R^{3d} is -C(Y¹)R^x, -C(Y¹)OR^x or -C(Y¹)(N(R^x)(R^x));
- 15 R⁴ is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;
- R⁵ is R⁴ wherein each R⁴ is substituted with 0 to 3 R³ groups;
- R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, 20 alkenylene or alkynylene is substituted with 0-3 R³ groups;
- W³ is W⁴ or W⁵;
- W⁴ is R⁵, -C(Y¹)R⁵, -C(Y¹)W⁵, -SO₂R⁵, or -SO₂W⁵;
- W⁵ is carbocycle or heterocycle wherein W⁵ is independently substituted with 0 to 3 R² groups;
- 25 W⁶ is W³ independently substituted with 1, 2, or 3 A³ groups;
- M2 is 0, 1 or 2;
- M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M1a, M1c, and M1d are independently 0 or 1;
- 30 M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and
- In another embodiment the invention provides a conjugate, which has any one of the following formulae:



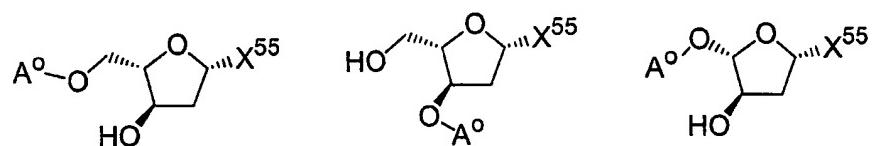
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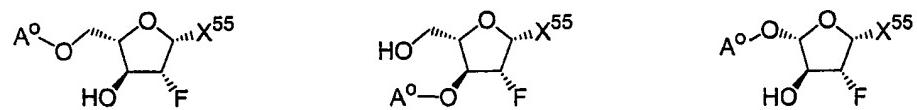
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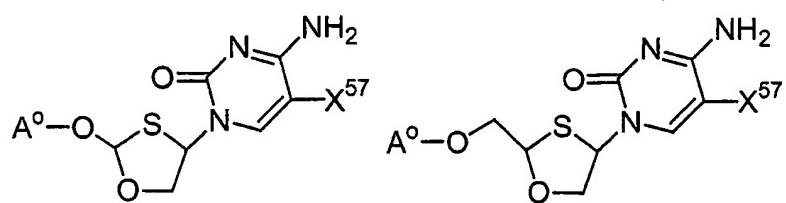
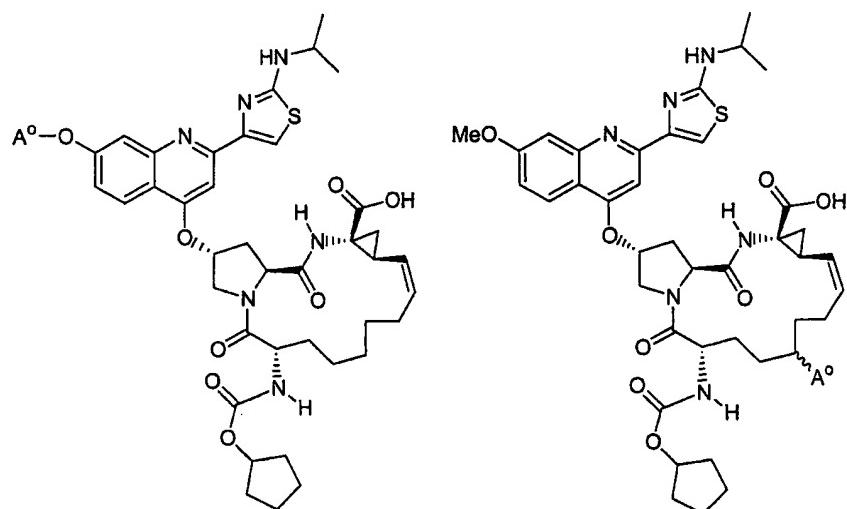
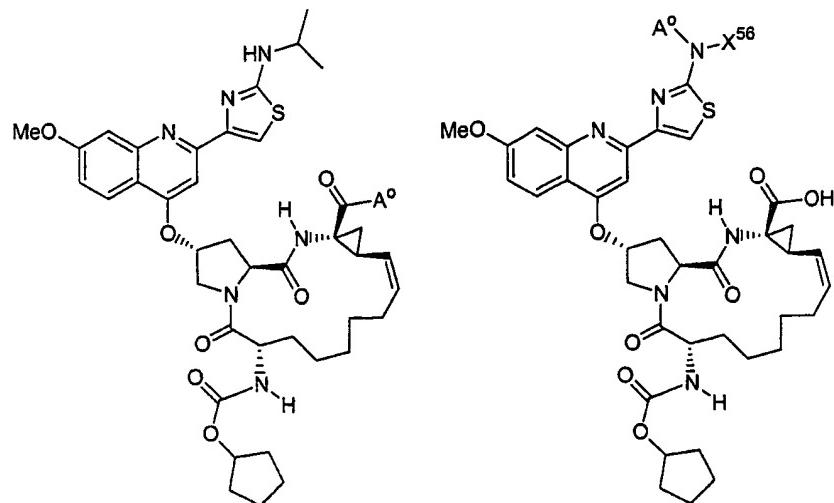


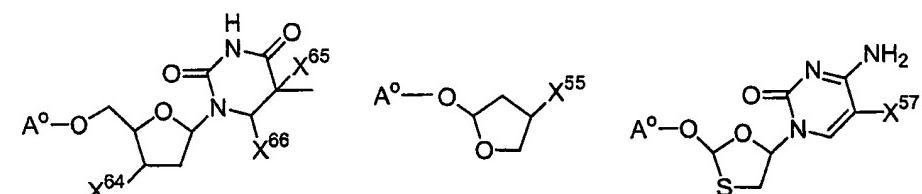
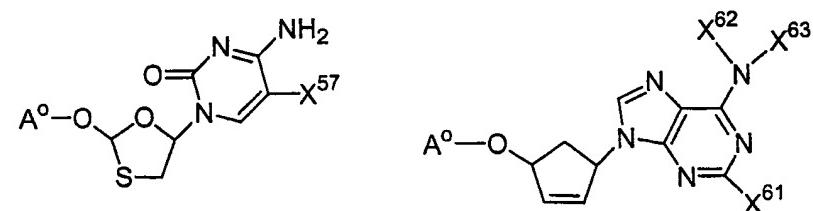
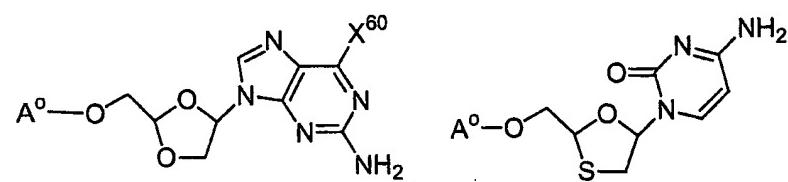
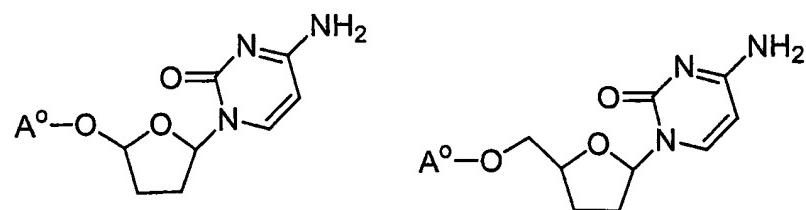
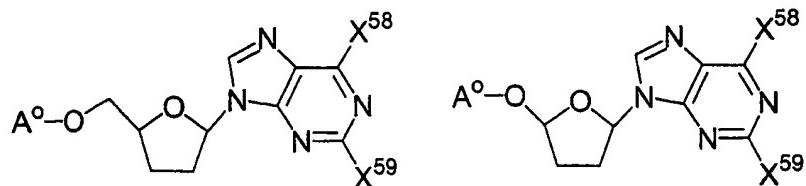
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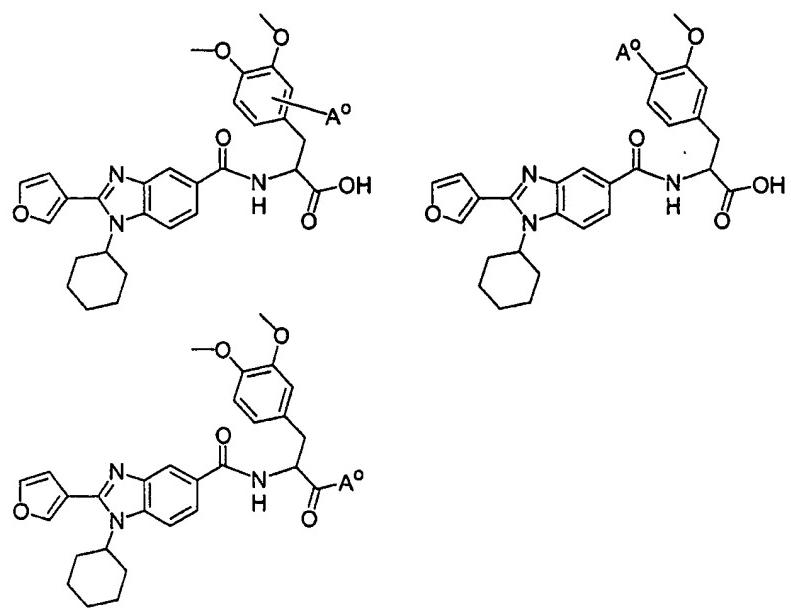


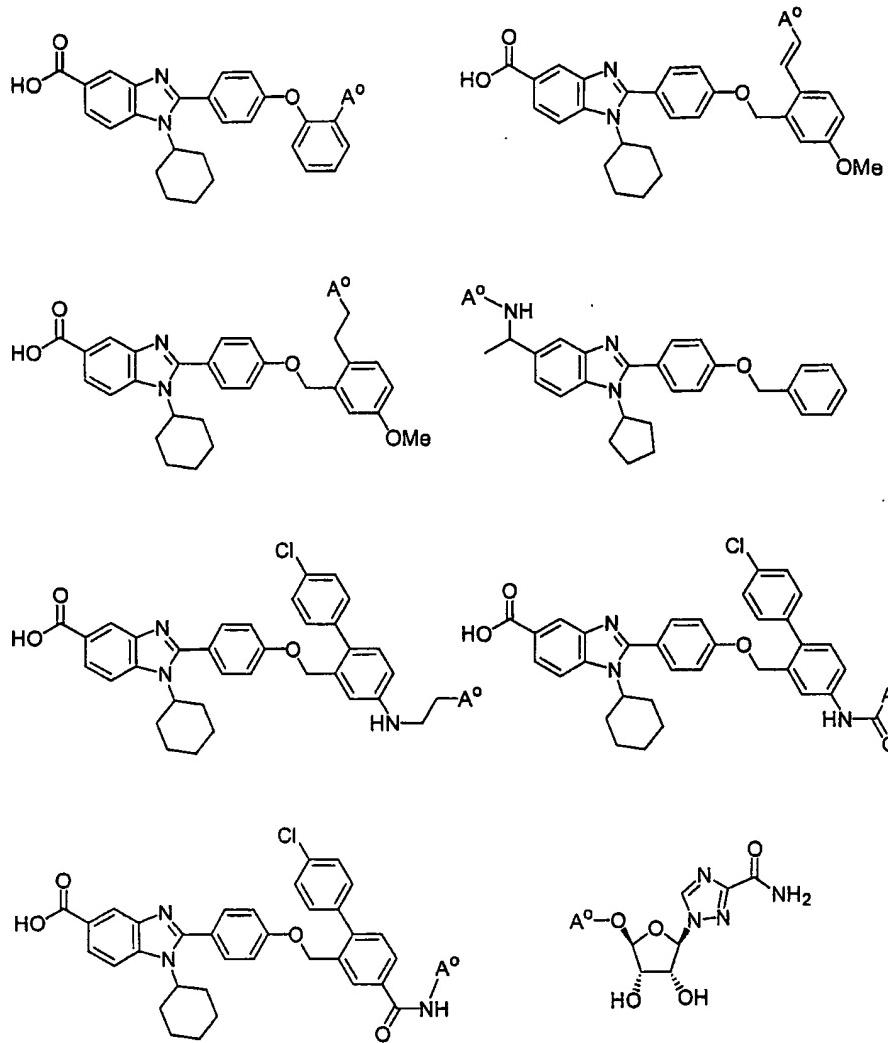
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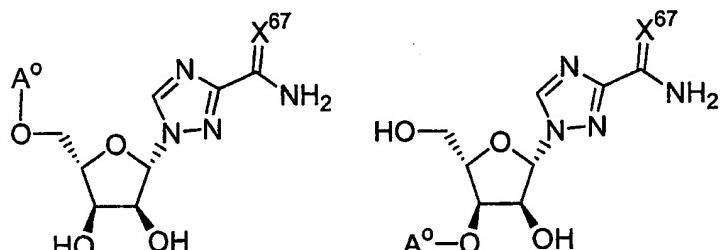
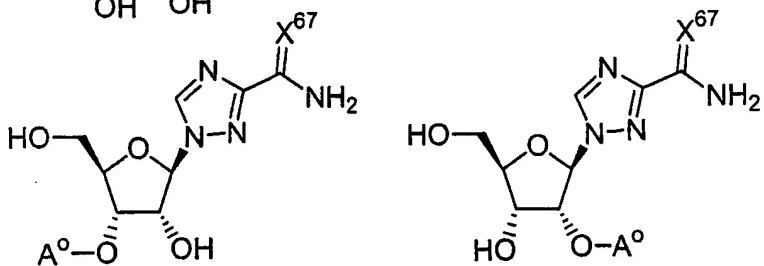
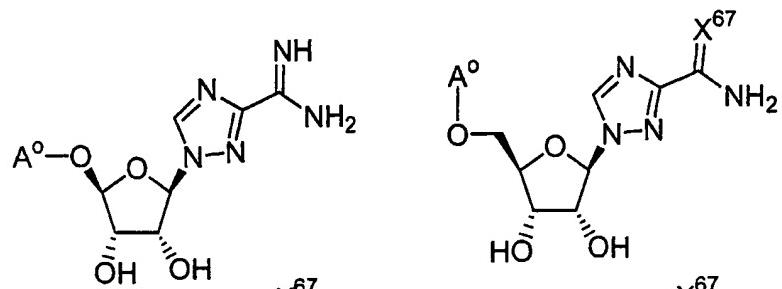
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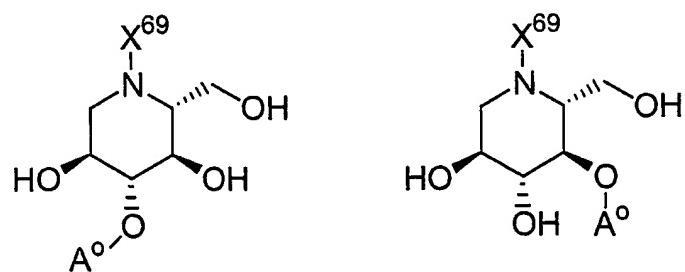
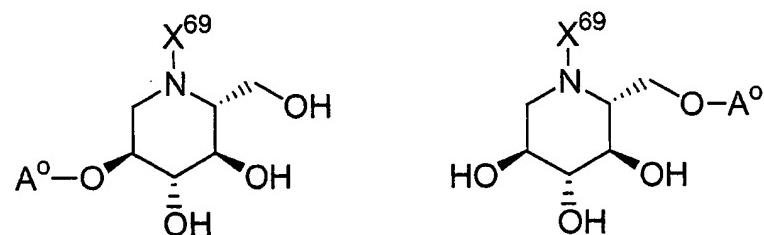


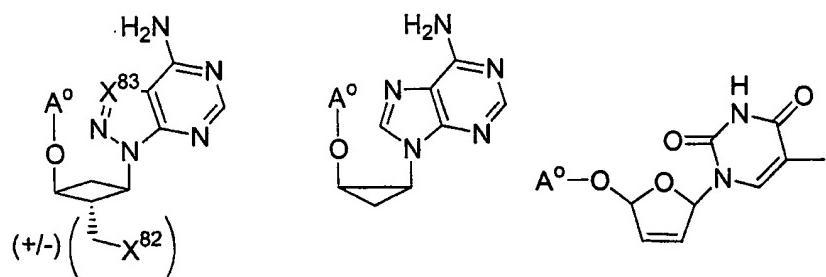
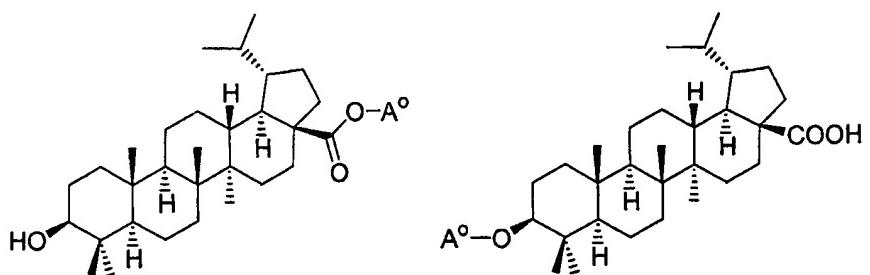
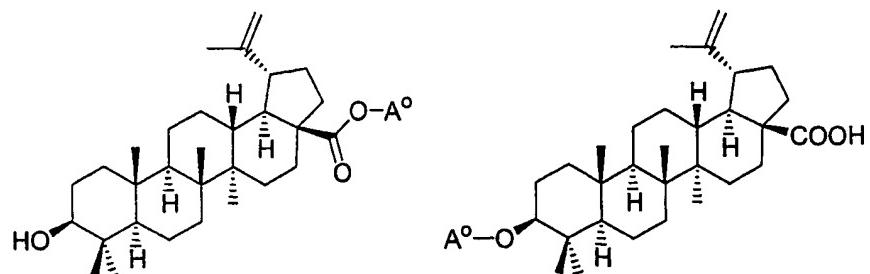




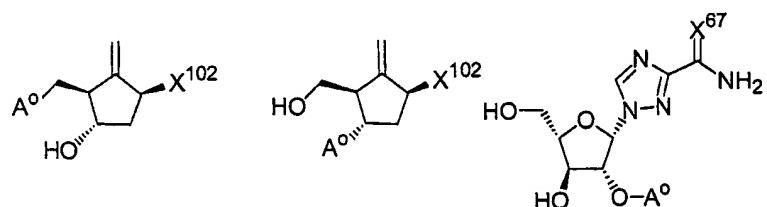
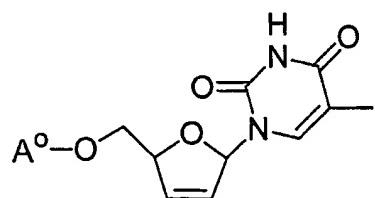


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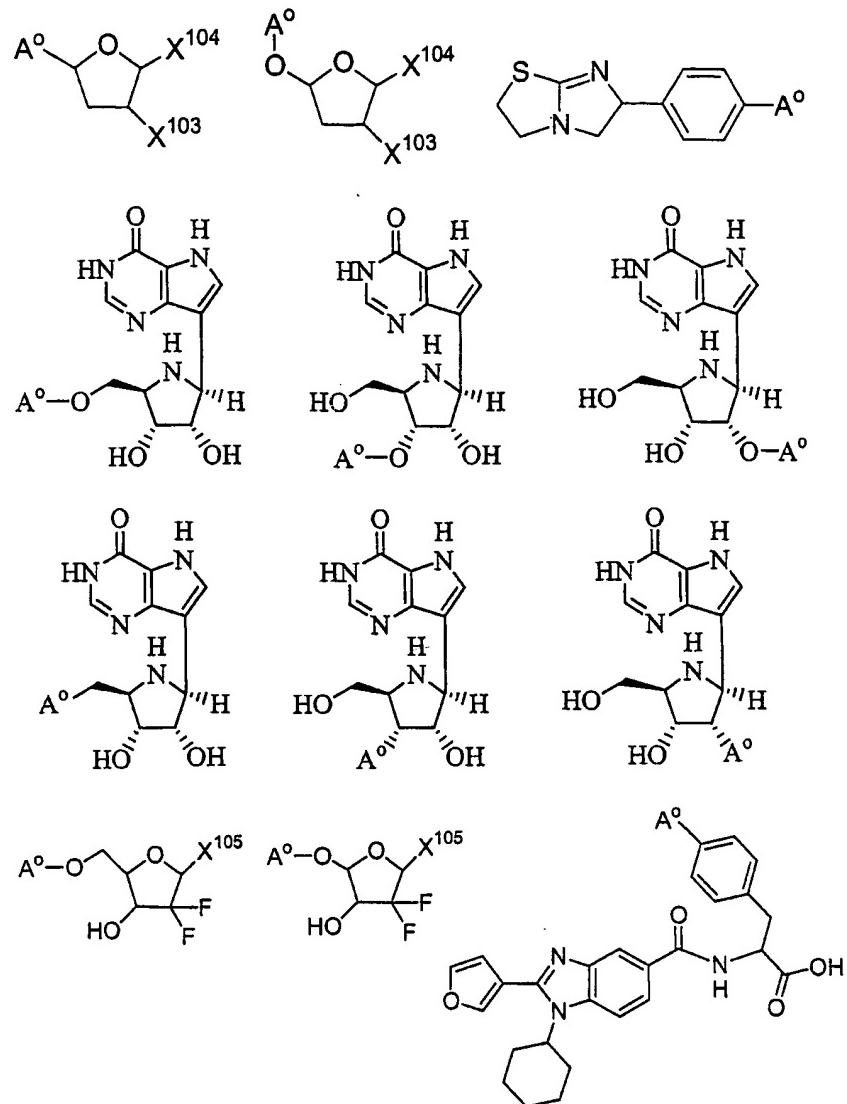




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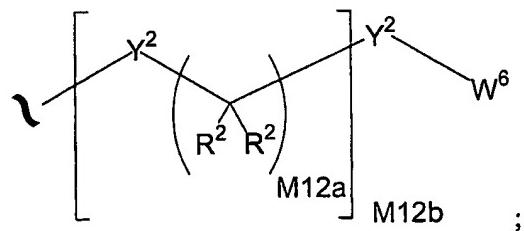
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wherein:

A^0 is A^1 , A^2 or W^3 with the proviso that one A^0 is A^1 ;

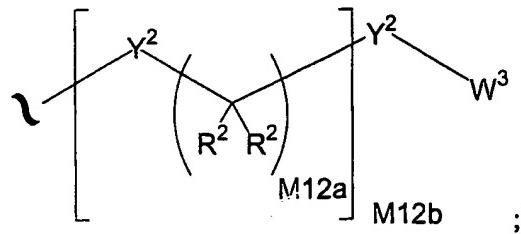
A^1 is:



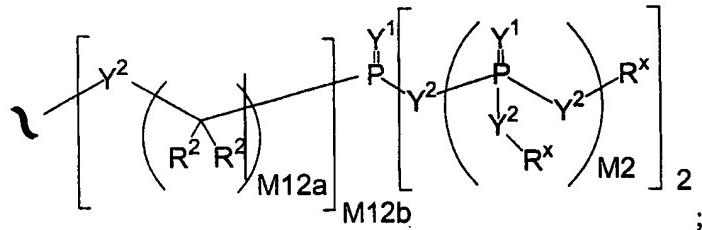
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A^2 is:

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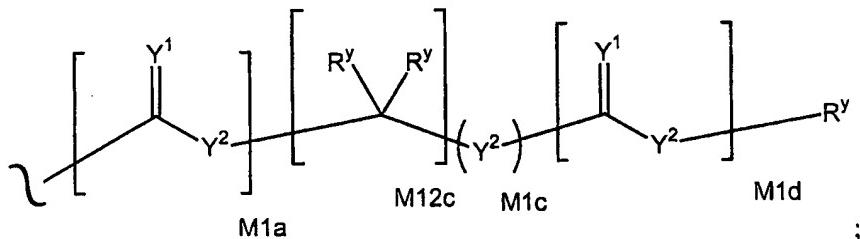
A^3 is:



5 Y^1 is independently O, S, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x), or N(N(R^x))(R^x);

Y^2 is independently a bond, O, N(R^x), N(O)(R^x), N(OR x), N(O)(OR x), N(N(R^x))(R^x)), -S(O) $_{\text{M}2}$ -S(O) $_{\text{M}2}$ -; and when Y^2 joins two phosphorous atoms Y^2 can also be C(R^2)(R^2);

10 R^x is independently H, R^1 , R^2 , W^3 , a protecting group, or the formula:



wherein:

R^y is independently H, W^3 , R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

15 R^2 is independently H, R^1 , R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a} , R^{3b} , R^{3c} or R^{3d} , provided that when R^3 is bound to a

20 heteroatom, then R^3 is R^{3c} or R^{3d} ;

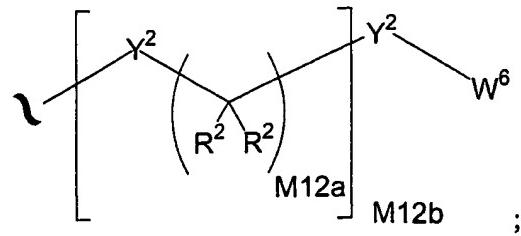
- R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;
- R^{3b} is Y^1 ;
- R^{3c} is $-R^X$, $-N(R^X)(R^X)$, $-SR^X$, $-S(O)R^X$, $-S(O)_2R^X$, $-S(O)(OR^X)$, $-S(O)_2(OR^X)$, $-OC(Y^1)R^X$, $-OC(Y^1)OR^X$, $-OC(Y^1)(N(R^X)(R^X))$, $-SC(Y^1)R^X$, $-SC(Y^1)OR^X$, $-SC(Y^1)(N(R^X)(R^X))$, $-N(R^X)C(Y^1)R^X$, $-N(R^X)C(Y^1)OR^X$, or $-N(R^X)C(Y^1)(N(R^X)(R^X))$;
- R^{3d} is $-C(Y^1)R^X$, $-C(Y^1)OR^X$ or $-C(Y^1)(N(R^X)(R^X))$;
- R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;
- 10 R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;
- R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;
- W^3 is W^4 or W^5 ;
- 15 W^4 is R^5 , $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;
- W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;
- W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;
- $M2$ is 0, 1 or 2;
- 20 M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- M1a, M1c, and M1d are independently 0 or 1;
- M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
- X^{51} is H, α -Br, or β -Br;
- 25 X^{52} is alkyl or a arylalkyl;
- X^{53} is H, C_1-C_4 alkyl;
- X^{54} is CH or N;
- X^{55} is thymine, adenine, uracil, 5-halouracils, 5-alkyluracils, guanine, cytosine, 5-halo and alkyl cytosines, or 2,6-diaminopurine;
- 30 X^{56} is H, Me, Et, or *i*-Pr;
- X^{57} is H or F;
- X^{58} is OH, Cl, NH_2 , H, Me, or MeO;

- X^{59} is H or NH₂;
- X^{60} is OH, Cl, NH₂, or H;
- X^{61} is H, NH₂, or NH-alkyl;
- X^{62} and X^{63} are independently H, alkyl, or cyclopropyl;
- 5 X^{64} is H, N₃, NH₂, or NHAc;
- X^{65} is a halo;
- X^{66} is alkoxy, aryloxy, alkenyloxy, arylalkoxy;
- X^{67} =O or =NH;
- X^{69} is H or alkyl;
- 10 X^{82} is OH, F, or cyano;
- X^{83} is N or CH;
- X^{102} is thymine, adenine, guanine, cytosine, uracil, inosine, or
diaminopurine;
- X^{103} is OH, alkoxy, CN, NO₂, F, Cl, Br, or I;
- 15 X^{104} is adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine,
- 20 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O⁶-methylguanine, N⁶-methyladenine, O⁴-methylthymine, 5,6-dihydrothymine, 5,6-dihydouracil, 4-methylindole, or pyrazolo[3,4-d]pyrimidine; and
- X^{105} is cytosine.

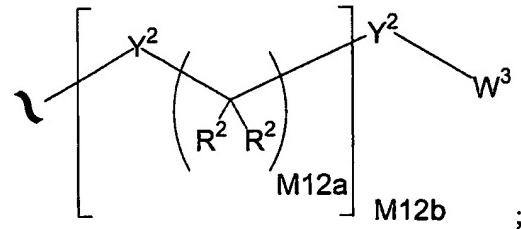
In one specific embodiment of the invention, the conjugate is a compound that is substituted with one or more phosphonate groups either directly or indirectly through a linker; and that is optionally substituted with one or more groups A⁰; or a pharmaceutically acceptable salt thereof, wherein:

A⁰ is A¹, A² or W³;

A¹ is:

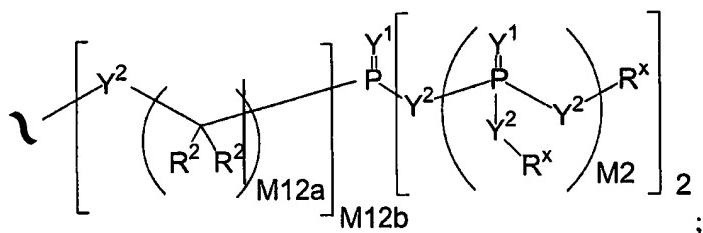


A² is:



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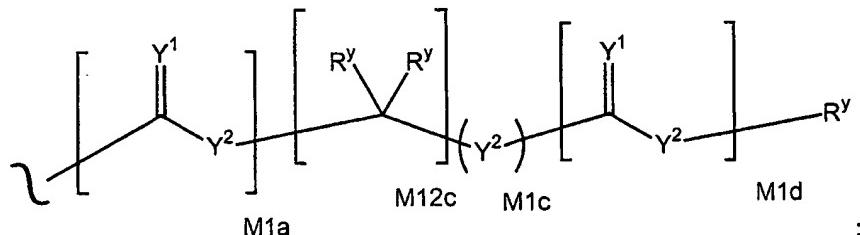
A³ is:



Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

10 Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)), -S(O)_{M2}- , or -S(O)_{M2}-S(O)_{M2}-;

R^x is independently H, R¹, W³, a protecting group, or the formula:



wherein:

15 R^y is independently H, W³, R² or a protecting group;

R¹ is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1 , R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

5 R^3 is R^{3a} , R^{3b} , R^{3c} or R^{3d} , provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d} ;

R^{3a} is F, Cl, Br, I, -CN, N₃ or -NO₂;

R^{3b} is Y¹;

R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)₂R^x, -S(O)(OR^x), -

10 S(O)₂(OR^x), -OC(Y¹)R^x, -OC(Y¹)OR^x, -OC(Y¹)(N(R^x)(R^x)), -SC(Y¹)R^x, -SC(Y¹)OR^x, -SC(Y¹)(N(R^x)(R^x)), -N(R^x)C(Y¹)R^x, -N(R^x)C(Y¹)OR^x, or -N(R^x)C(Y¹)(N(R^x)(R^x));

R^{3d} is -C(Y¹)R^x, -C(Y¹)OR^x or -C(Y¹)(N(R^x)(R^x));

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms,

15 or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

20 W³ is W⁴ or W⁵;

 W⁴ is R⁵, -C(Y¹)R⁵, -C(Y¹)W⁵, -SO₂R⁵, or -SO₂W⁵;

 W⁵ is carbocycle or heterocycle wherein W⁵ is independently substituted with 0 to 3 R^2 groups;

 W⁶ is W³ independently substituted with 1, 2, or 3 A³ groups;

25 M2 is 0, 1 or 2;

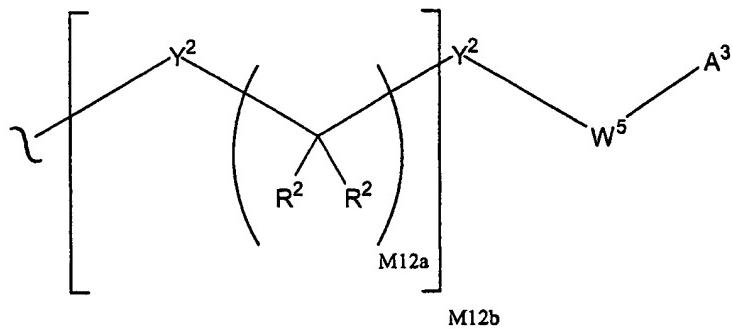
 M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

 M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

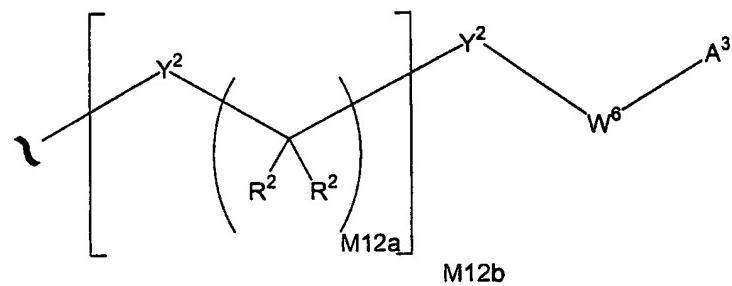
 M1a, M1c, and M1d are independently 0 or 1; and

 M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

30 In another specific embodiment of the invention A¹ is of the formula:

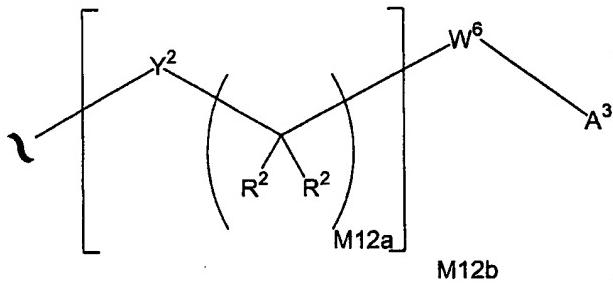


In another specific embodiment of the invention A¹ is of the formula:

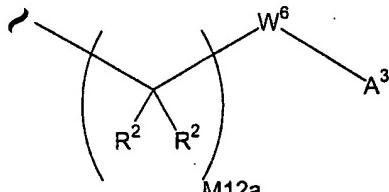


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In another specific embodiment of the invention A¹ is of the formula:

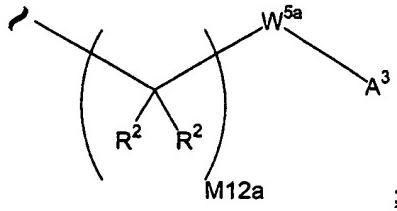


In another specific embodiment of the invention A¹ is of the formula:



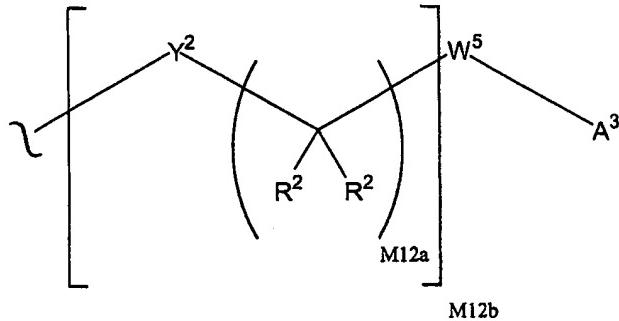
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In another specific embodiment of the invention A¹ is of the formula:

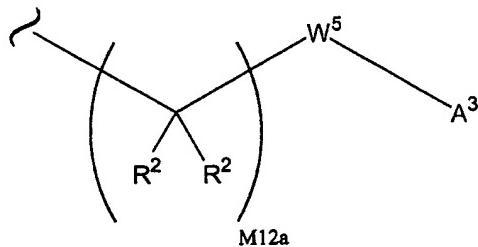


and W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R² groups. A specific value for M12a is 1.

5 In another specific embodiment of the invention A¹ is of the formula:

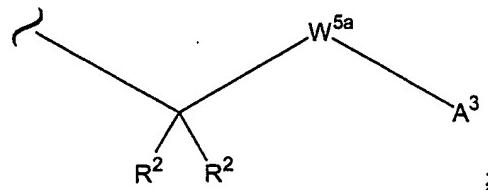


In another specific embodiment of the invention A¹ is of the formula:



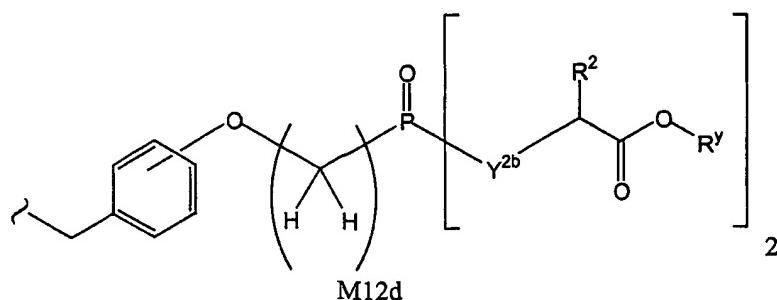
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In another specific embodiment of the invention A¹ is of the formula:



wherein W^{5a} is a carbocycle independently substituted with 0 or 1 R² groups;

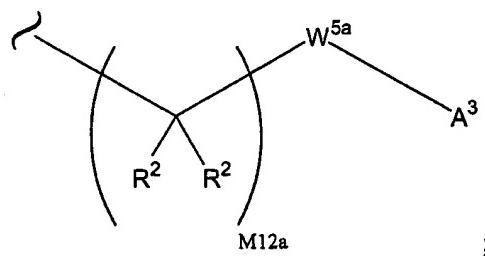
15 In another specific embodiment of the invention A¹ is of the formula:



wherein Y^{2b} is O or N(R²); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

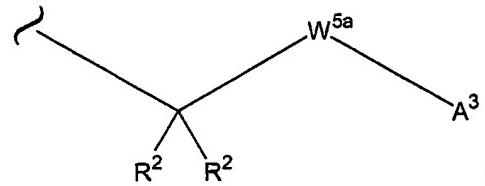
In another specific embodiment of the invention A¹ is of the formula:

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wherein W^{5a} is a carbocycle independently substituted with 0 or 1 R² groups;

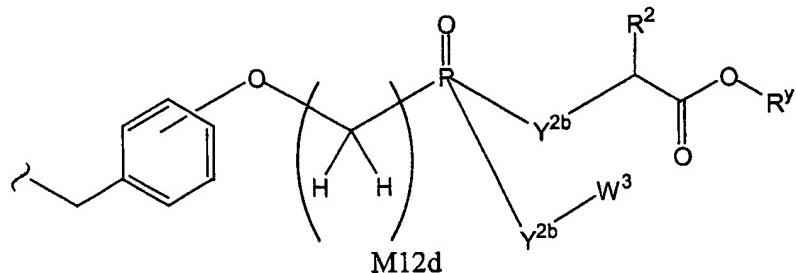
In another specific embodiment of the invention A¹ is of the formula:



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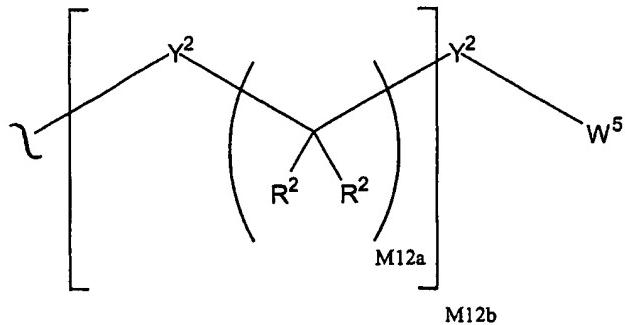
wherein W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R² groups.

In another specific embodiment of the invention A¹ is of the formula:



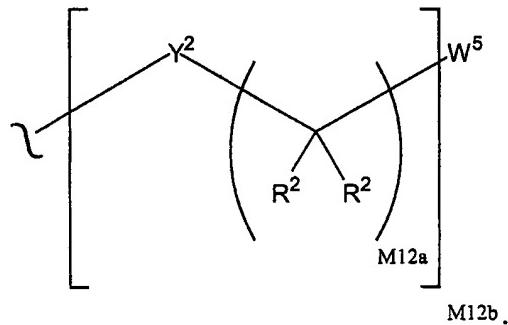
wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In a specific embodiment of the invention A^2 is of the formula:



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In another specific embodiment of the invention A^2 is of the formula:

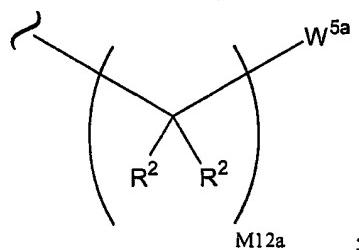


In another specific embodiment of the invention M12b is 1.

10 In another specific embodiment of the invention e M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^2 is of the formula:

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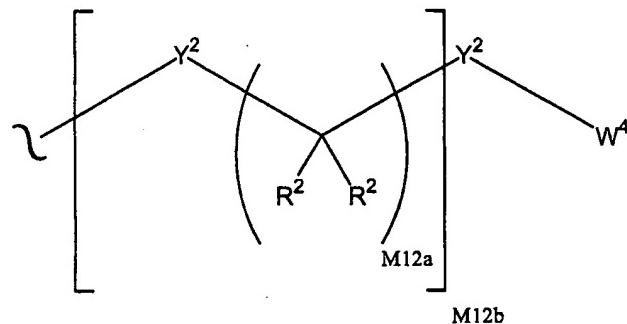


wherein W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention M12a is 1.

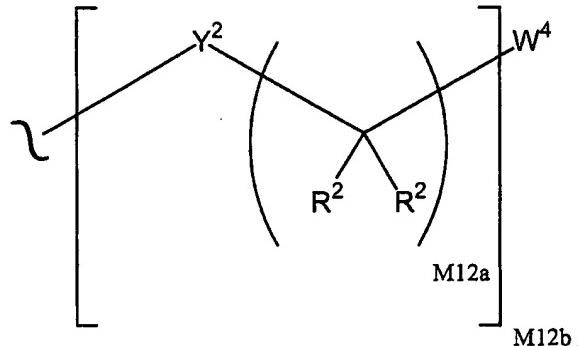
- 5 In another specific embodiment of the invention A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

In another specific embodiment of the invention A^2 is of the formula:



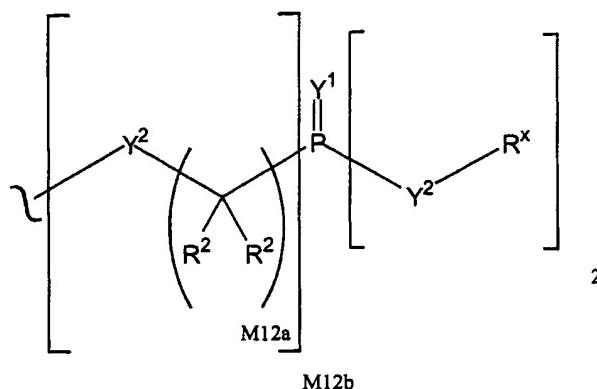
10

In another specific embodiment of the invention A^2 is of the formula:

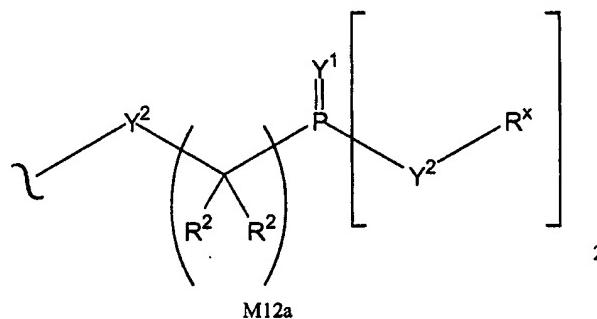


In another specific embodiment of the invention M12b is 1.

In a specific embodiment of the invention A^3 is of the formula:

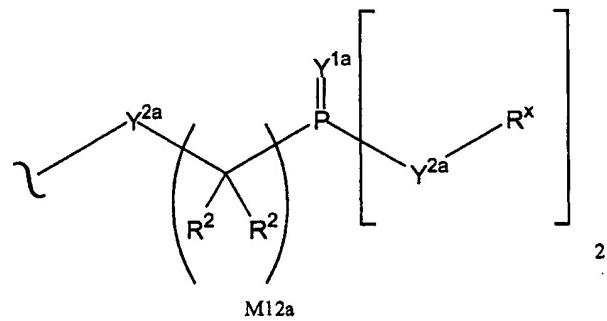


In another specific embodiment of the invention A³ is of the formula:



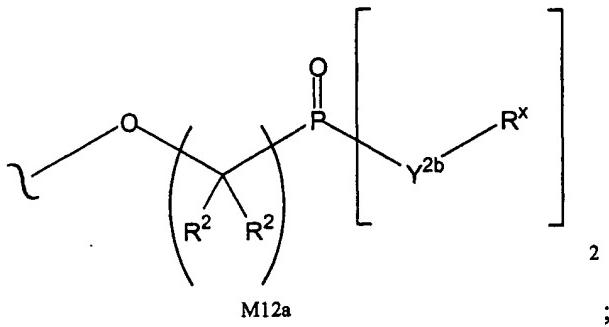
5

In another specific embodiment of the invention A³ is of the formula:



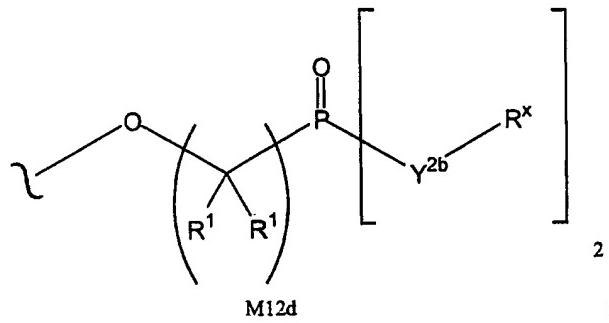
wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^x) or S.

In another specific embodiment of the invention A³ is of the formula:



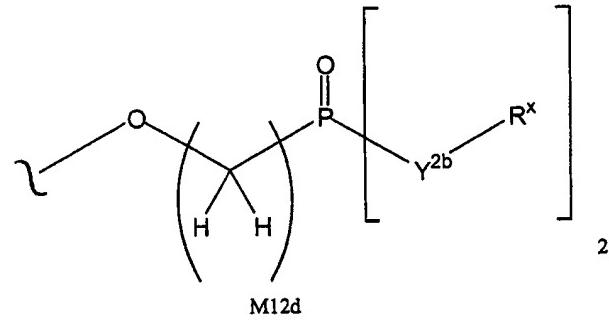
wherein Y^{2b} is O or N(R^x).

In another specific embodiment of the invention A³ is of the formula:



5 wherein Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

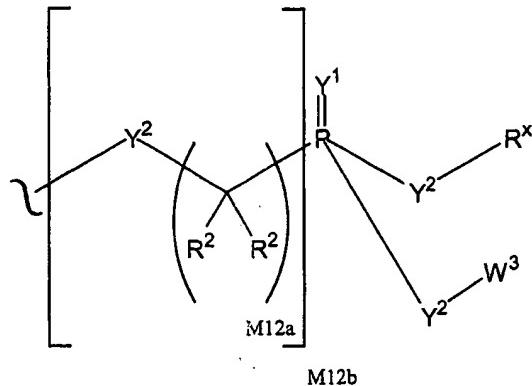
In another specific embodiment of the invention A³ is of the formula:



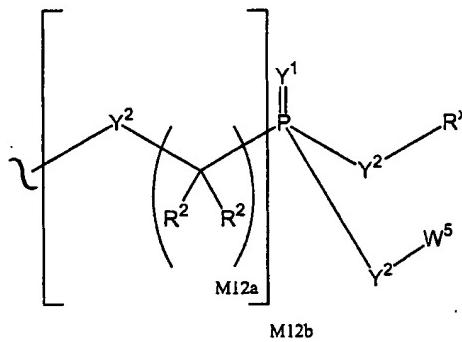
wherein Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention M12d is 1.

10 In another specific embodiment of the invention A³ is of the formula:



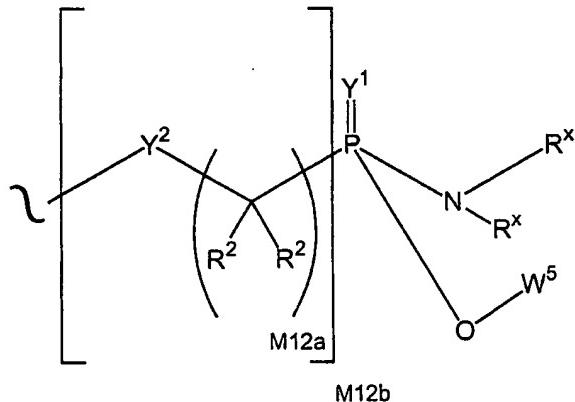
In another specific embodiment of the invention A³ is of the formula:



5

In another specific embodiment of the invention W⁵ is a carbocycle.

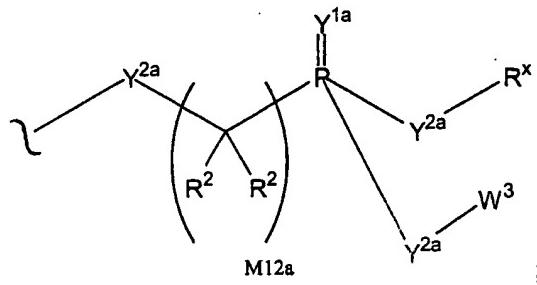
In another specific embodiment of the invention A³ is of the formula:



10

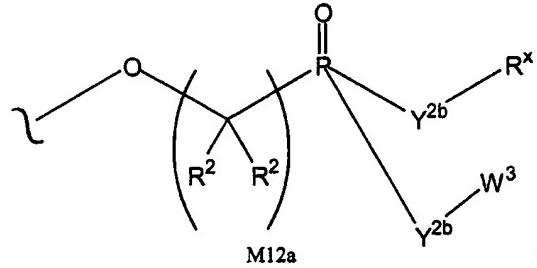
In another specific embodiment of the invention W⁵ is phenyl.

In another specific embodiment of the invention A³ is of the formula:



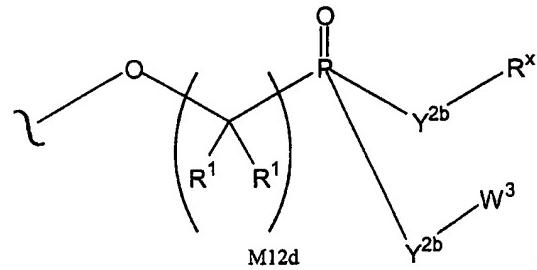
wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^x) or S.

In another specific embodiment of the invention A³ is of the formula:



5 wherein Y^{2b} is O or $N(R^x)$.

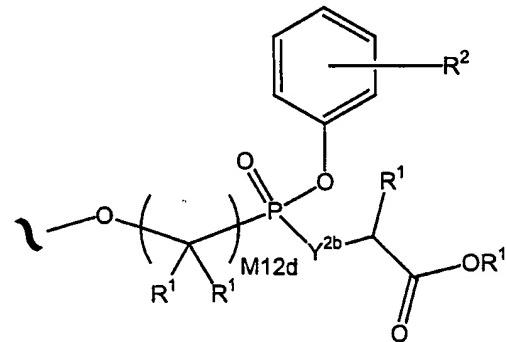
In another specific embodiment of the invention A³ is of the formula:



wherein Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

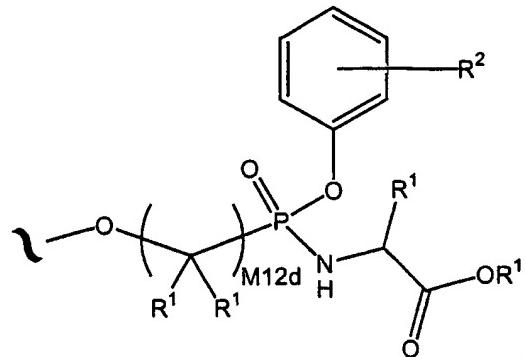
In another specific embodiment of the invention R¹ is H.

10 In another specific embodiment of the invention A³ is of the formula:



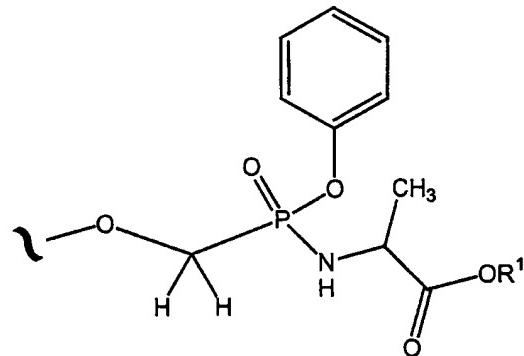
wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R² groups.

In another specific embodiment of the invention A³ is of the formula:

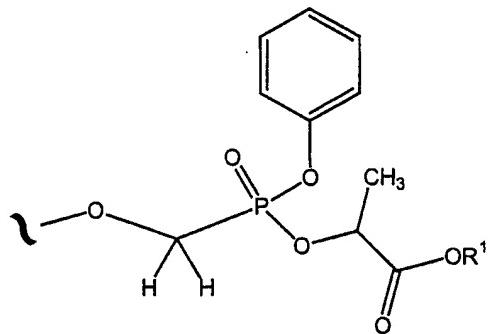


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In another specific embodiment of the invention A³ is of the formula:

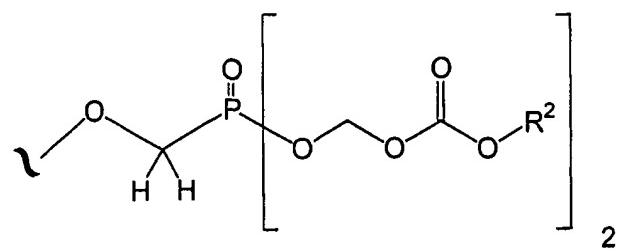


In another specific embodiment of the invention A³ is of the formula:

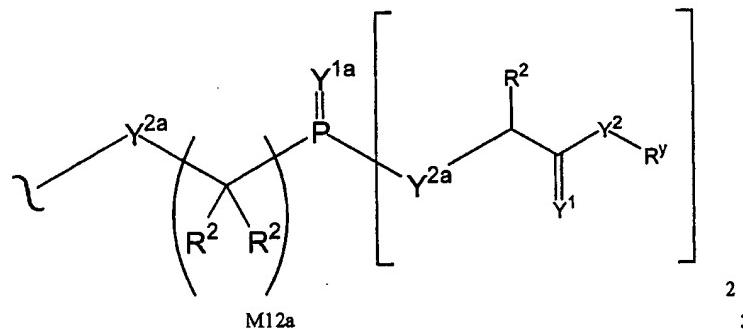


10

In another specific embodiment of the invention A³ is of the formula:

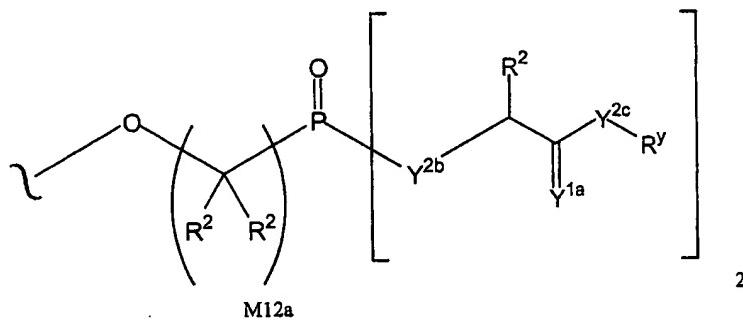


In another specific embodiment of the invention A³ is of the formula:



5 wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^2) or S.

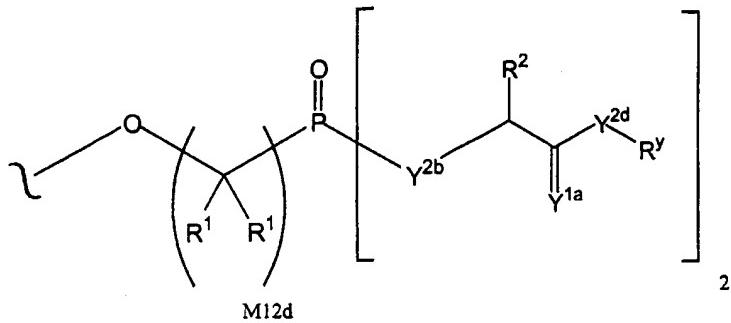
In another specific embodiment of the invention A³ is of the formula:



wherein Y^{1a} is O or S; Y^{2b} is O or N(R²); and Y^{2c} is O, N(R^y) or S.

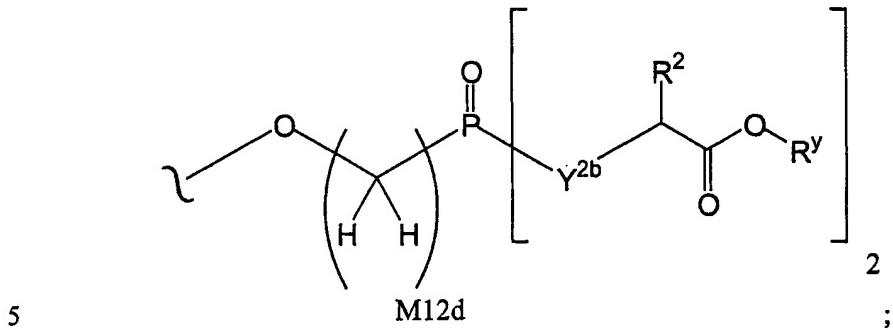
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In another specific embodiment of the invention A³ is of the formula:



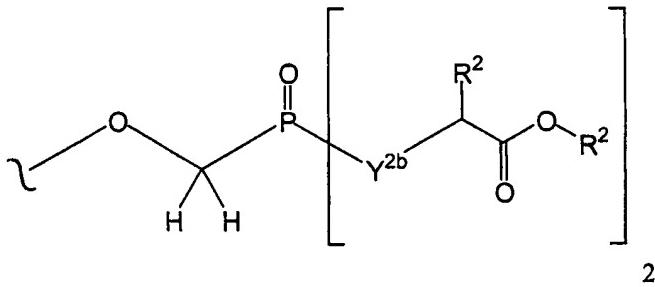
wherein Y^{1a} is O or S; Y^{2b} is O or $N(R^2)$; Y^{2d} is O or $N(R^y)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A³ is of the formula:



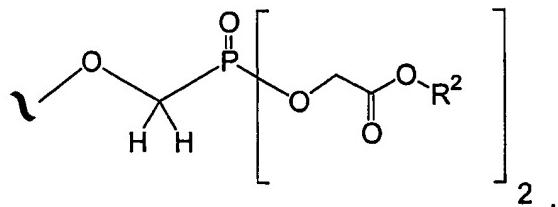
wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A³ is of the formula:

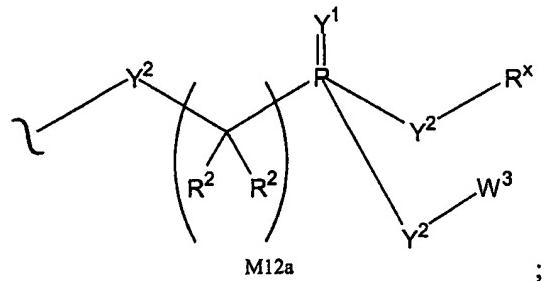


10 wherein Y^{2b} is O or $N(R^2)$.

In another specific embodiment of the invention A³ is of the formula:

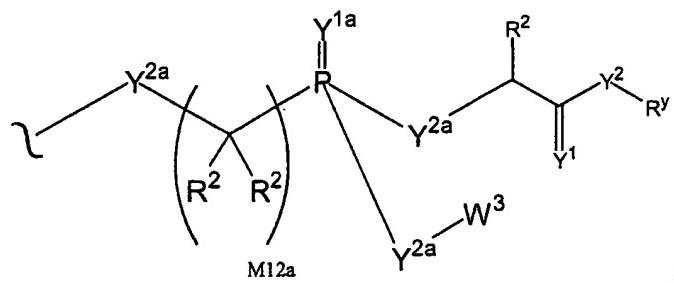


In another specific embodiment of the invention A³ is of the formula:



5

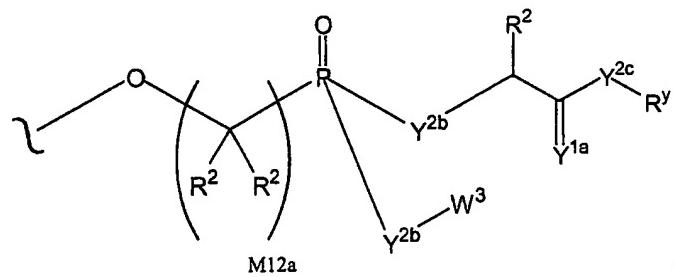
In another specific embodiment of the invention A³ is of the formula:



wherein Y^{1a} is O or S; and Y^{2a} is O, N(R²) or S.

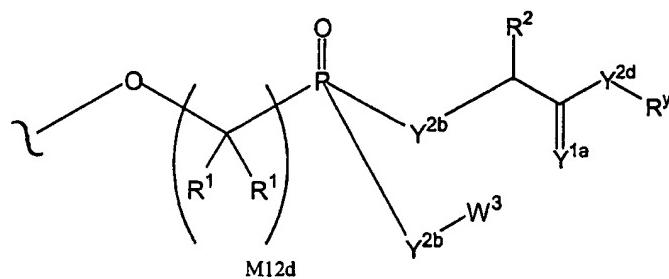
In another specific embodiment of the invention A³ is of the formula:

10



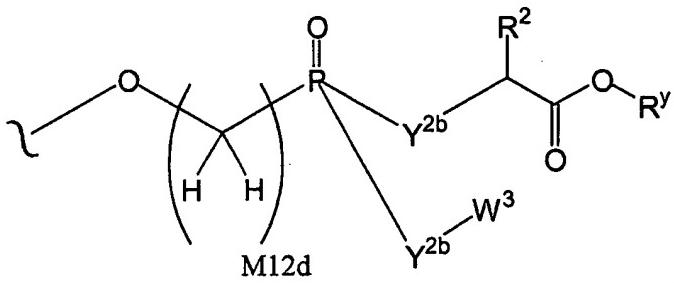
wherein Y^{1a} is O or S; Y^{2b} is O or N(R²); and Y^{2c} is O, N(R^y) or S.

In another specific embodiment of the invention A³ is of the formula:



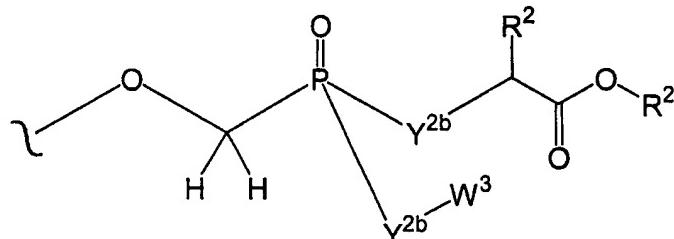
wherein Y^{1a} is O or S; Y^{2b} is O or $N(R^2)$; Y^{2d} is O or $N(R^y)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

5 In another specific embodiment of the invention A^3 is of the formula:



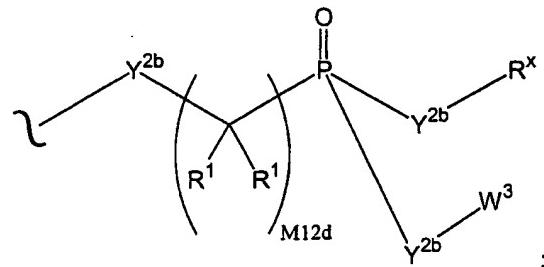
wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:



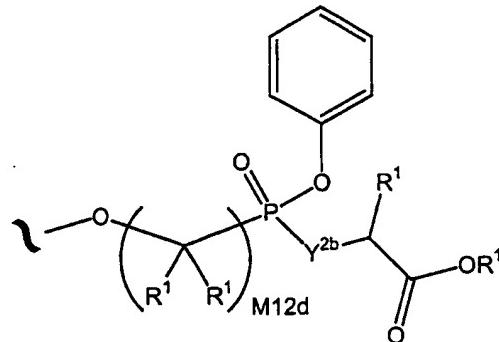
10 wherein Y^{2b} is O or $N(R^2)$.

In another specific embodiment of the invention A^3 is of the formula:



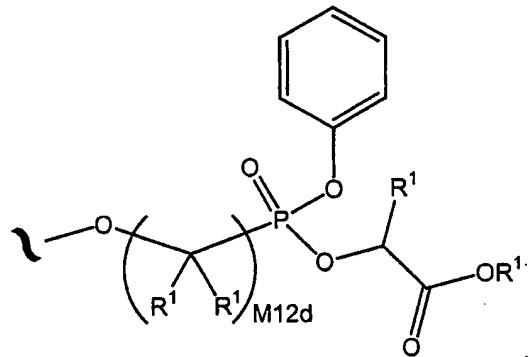
wherein: Y^{2b} is O or $N(R^x)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A³ is of the formula:



wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R² groups.

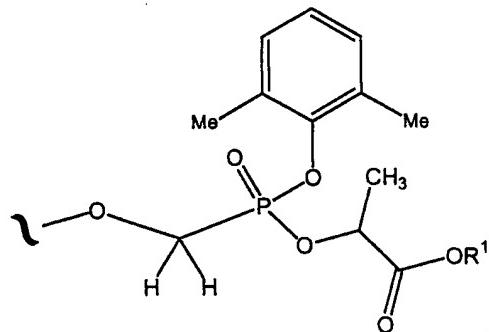
In another specific embodiment of the invention A³ is of the formula:



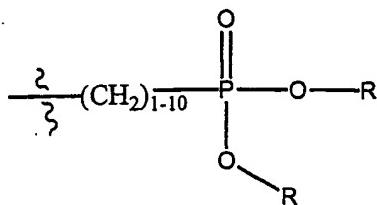
5

wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R² groups.

In another specific embodiment of the invention A³ is of the formula:



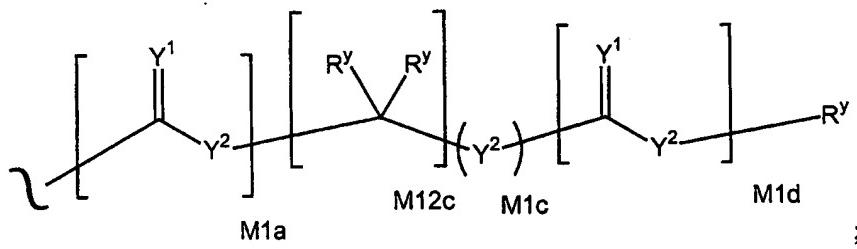
In a specific embodiment of the invention A⁰ is of the formula:



wherein each R is independently (C₁-C₆)alkyl.

In a specific embodiment of the invention R^x is independently H, R¹, W³, a protecting group, or the formula:

5



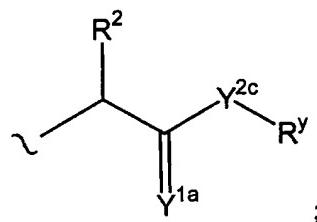
wherein:

R^y is independently H, W³, R² or a protecting group;

R¹ is independently H or alkyl of 1 to 18 carbon atoms;

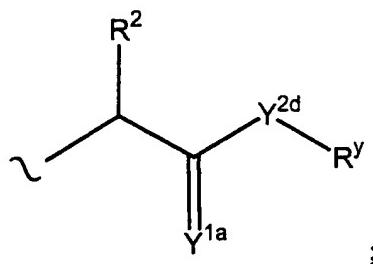
R² is independently H, R¹, R³ or R⁴ wherein each R⁴ is independently substituted with 0 to 3 R³ groups or taken together at a carbon atom, two R² groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R³ groups.

In a specific embodiment of the invention R^x is of the formula:



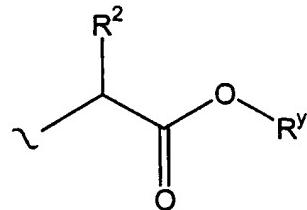
15 wherein Y^{1a} is O or S; and Y^{2c} is O, N(R^y) or S.

In a specific embodiment of the invention R^x is of the formula:



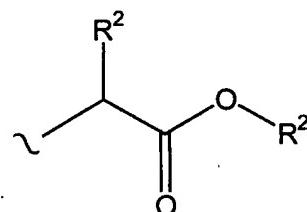
wherein Y^{1a} is O or S; and Y^{2d} is O or N(R^y).

In a specific embodiment of the invention R^x is of the formula:

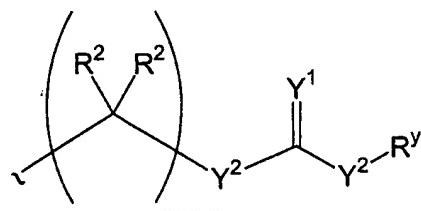


5 In a specific embodiment of the invention R^y is hydrogen or alkyl of 1 to 10 carbons.

In a specific embodiment of the invention R^x is of the formula:

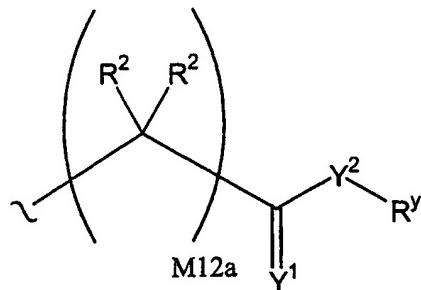


In a specific embodiment of the invention R^x is of the formula:



10

In a specific embodiment of the invention R^x is of the formula:

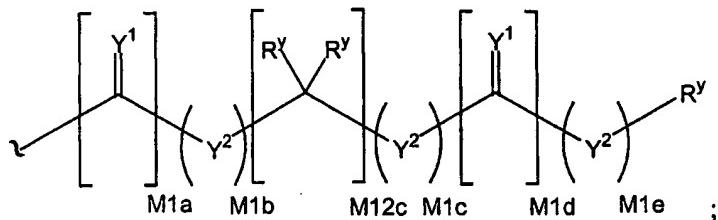


In a specific embodiment of the invention Y^1 is O or S

In a specific embodiment of the invention Y^2 is O, N(R^y) or S.

In one specific embodiment of the invention R^x is a group of the formula:

5



wherein:

$m1a, m1b, m1c, m1d$ and $m1e$ are independently 0 or 1;

$m12c$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

R^y is H, W^3 , R^2 or a protecting group;

10 *provided that:*

if $m1a, m12c$, and $m1d$ are 0, then $m1b, m1c$ and $m1e$ are 0;

if $m1a$ and $m12c$ are 0 and $m1d$ is not 0, then $m1b$ and $m1c$ are 0;

if $m1a$ and $m1d$ are 0 and $m12c$ is not 0, then $m1b$ and at least one of $m1c$ and $m1e$ are 0;

15 if $m1a$ is 0 and $m12c$ and $m1d$ are not 0, then $m1b$ is 0;

if $m12c$ and $m1d$ are 0 and $m1a$ is not 0, then at least two of $m1b, m1c$ and $m1e$ are 0;

if $m12c$ is 0 and $m1a$ and $m1d$ are not 0, then at least one of $m1b$ and $m1c$ are 0; and

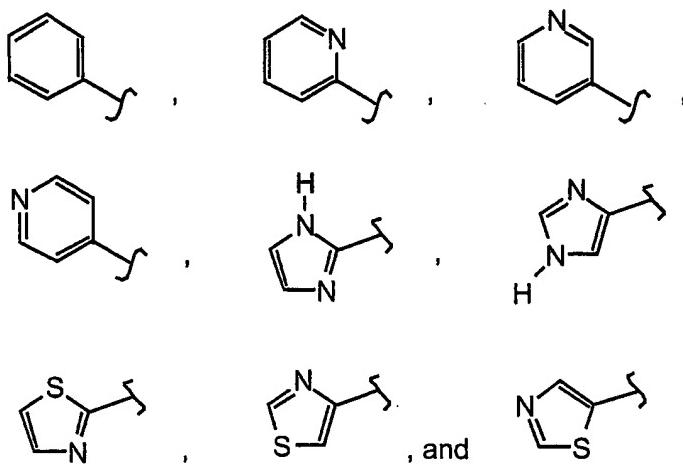
20 if $m1d$ is 0 and $m1a$ and $m12c$ are not 0, then at least one of $m1c$ and $m1e$ are 0.

In compounds of the invention W^5 carbocycles and W^5 heterocycles may be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated,

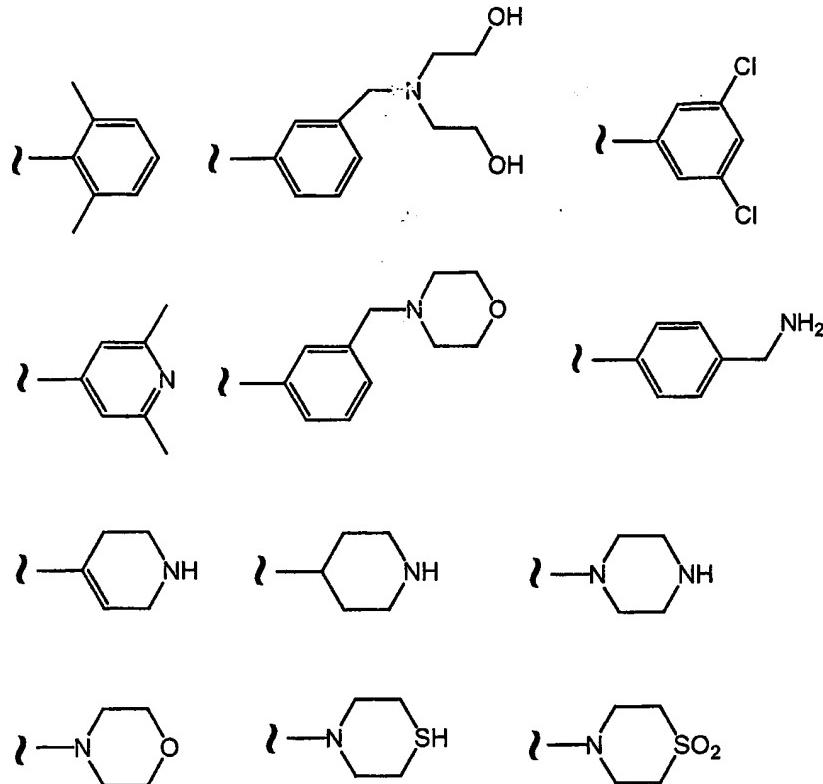
unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thifuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:

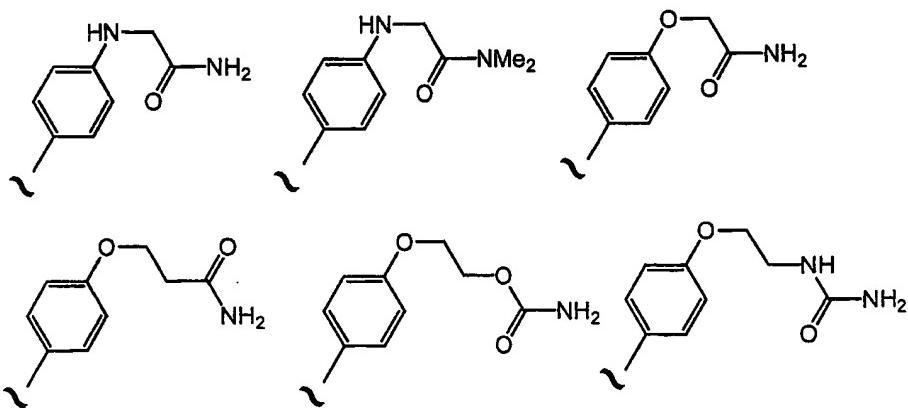


W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:



5

Examples of substituted phenyl carbocycles include:



Linking Groups and Linkers

- 10 The invention provides conjugates that comprise a therapeutic compound that is linked to one or more phosphonate groups either directly (*e.g.* through a

covalent bond) or through a linking group (*i.e.* a linker). The nature of the linker is not critical provided it does not interfere with the ability of the phosphonate containing compound to function as a therapeutic agent. The phosphonate or the linker can be linked to the compound at any synthetically feasible position on the 5 compound by removing a hydrogen or any portion of the compound to provide an open valence for attachment of the phosphonate or the linker.

In one embodiment of the invention the linking group or linker (which can be designated "L") can include all or a portions of the group A⁰, A¹, A², A³, or W³ described herein, such as for example, repeating units of alkyloxy (*e.g.*, 10 polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (*e.g.*, polyethyleneamino, JeffamineTM); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

In another embodiment of the invention the linking group or linker has a molecular weight of from about 20 daltons to about 400 daltons.

15 In another embodiment of the invention the linking group or linker has a length of about 5 angstroms to about 300 angstroms.

In another embodiment of the invention the linking group or linker separates the DRUG and the phosphorous of the phosphonate group by about 5 angstroms to about 200 angstroms, inclusive, in length.

20 In another embodiment of the invention the linking group or linker is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (*e.g.* 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-), and wherein the chain is optionally substituted on carbon with one or more (*e.g.* 1, 2, 3, or 4) substituents selected 25 from (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyl, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

In another embodiment of the invention the linking group or linker is of the formula W-A wherein A is (C₁-C₂₄)alkyl, (C₂-C₂₄)alkenyl, (C₂-C₂₄)alkynyl, 30 (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl or a combination thereof, wherein W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-,

N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

In another embodiment of the invention the linking group or linker is a divalent radical formed from a peptide.

- 5 In another embodiment of the invention the linking group or linker is a divalent radical formed from an amino acid.

In another embodiment of the invention the linking group or linker is a divalent radical formed from poly-L-glutamic acid, poly-L-aspartic acid, poly-L-histidine, poly-L-ornithine, poly-L-serine, poly-L-threonine, poly-L-tyrosine, 10 poly-L-leucine, poly-L-lysine-L-phenylalanine, poly-L-lysine or poly-L-lysine-L-tyrosine.

- In another embodiment of the invention the linking group or linker is of the formula W-(CH₂)_n wherein, n is between about 1 and about 10; and W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-,-C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

In another embodiment of the invention the linking group or linker is methylene, ethylene, or propylene.

- 20 In another embodiment of the invention the linking group or linker is attached to the phosphonate group through a carbon atom of the linker.

Intracellular Targeting

The phosphonate group of the compounds of the invention may cleave *in vivo* in stages after they have reached the desired site of action, *i.e.* inside a cell.

- 25 One mechanism of action inside a cell may entail a first cleavage, *e.g.* by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in a compound of the invention thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.
- 30 After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate or prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a "trapping"

mechanism. The cleaved or modified compound may then be "locked-in" the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect are achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

- From the foregoing, it will be apparent that many different drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

Therapeutic Compounds

- The compounds of the invention include those with therapeutic activity. The compounds of the inventions bear one or more (e.g. 1, 2, 3, or 4) phosphonate groups, which may be or may include a prodrug moiety (e.g., a phosphonate diester, phosphonamidate-ester prodrug, or a phosphondiamidate-ester (Jiang et al., US 2002/0173490 A1).

- The term "therapeutic" includes those compounds having therapeutic activity. In one embodiment of the invention, the compound is an anti-inflammatory compound; in one embodiment, the compound is a purine nucleoside phosphorylase inhibitor; in one embodiment the compound is an anti-cancer compound; in one embodiment the compound is active against immune-mediated conditions; in one embodiment the compound is active against metabolic diseases; in one embodiment the compound is an antiviral compound; in one embodiment the compound is a nucleoside or nucleoside analog; in one embodiment the compound is a kinase inhibitor; in one embodiment the

compound is an antimetabolite; in one embodiment the compound is an IMPDH inhibitor; and in one embodiment the compound is an anti-infective compound.

Anti-inflammatory compounds include theophylline, methylxanthine, metamizole, rofecoxib, meloxicam, piroxicam, valdecoxib, tenoxicam,

- 5 celecoxib, etodolac, etoricoxib, ibuprofin, naproxen, loxoprofen, diclofenac, relafen, mefenamic acid, nimesulide, aspirin, oxaprozin, toradol, R ketorolac, steroid phosphonates, pimecrolimus, everolimus, sirolimus, ralitrexed (tomudex), parecoxib, nimesulide, aminopterin, lumiracoxib, tacrolimus, prednisolone, rolipram, CC-1088, CDP 840, cilomilast, piclamilast, roflumilast, 10 atizoram, VX-148, brequinar, diflunisal, doramapimod, tolfenamic acid, droxicam, flurbiprofen, indomethacin, lornoxicam, NCX-701, 10-propargyl-10-deaza-aminopterin (PDX), talniflumate, thalidomide, dexketoprofen, zardaverine, nabumetone, licofelone, ketorolac, BCX-1777, amtolmetine guacil, aceclofenac, metoxibutropate, rubitecan, oxaprozin, sulindac, revimid, diprolene, 15 aclometasone, hydrocortisone, vanceril, leflunomide, methylprednisolone suleptanate, prednisone, clobetasol, SMP-114, teriflunomide, salicylic acid, etoricoxib, L-791,943, halobetasol propionate, ciclesonide, deflazacort, flunisolide, medroxyprogesterone, triamcinolone acetonide, rimexolone, fluticasone, mometasone furoate, methylprednisolone suleptanate, 20 beclometasone, methylprednisolone aceponate, merimepodib, mycophenolate, budesonide, dexamethasone, brequinar, immunosuppressive macrolide, methotrexate, zileuton, PNP-405, MDL-74428, prodrugs of 9- (3,3-dimethyl-5-phosphonopentyl) guanine, prodrugs of DADME-IMMG, leflunomide, and zardaverine.

- 25 Antiviral compounds include dehydroepiandrosterone, LY-582563, L-Fd4C, L-FddC, telbivudine, clevudine, macrocyclic protease inhibitors, dOTCP, dOTC, DDL DDLP, ddcP, ddC, DADP, DAPD, d4TP, D4T, 3TC, 3TCP FTCP, ABCP, AZT, IsoddAP, FTC, HCV polymerase inhibitors, JT scaffold for HCV polymerase inhibitors, ribavirin, viramidine, L-enantiomers of ribavirin and 30 viramidine, levovirin, alkovirs, imiquimod, resquimod, 4- (3-benzyl-phenyl)-2-hydroxy-4-oxo-but-2-enoic acid, propenone derivatives having HIV inhibiting activities, aza, polyazanaphthalenyl carboxamides, betulinic acid,

dihydrobetulinic acid, isodd a, d- and l-nucleosides, UT-231B, nucleosides, VX-148, gemcitabine, merimepodib, levamisole, mycophenolate, entecavir, antiviral prodrugs, foscarnet, carbovir, abacavir, and BCX-1777.

Compounds active against immune-mediated conditions include

- 5 pimecrolimus, everolimus, sirolimus, tacrolimus, prednisolone, VX-148, merimepodib, brequinar, thalidomide, BCX-1777, revimid, diprolene, aclometasone dipropionate, hydrocortisone, dexamethasone, leflunomide, methylprednisolone suleptanate, prednisone, clobetasol, MNA-715 (FK778), SMP-114, teriflunomide, halobetasol, ciclesonide, deflazacort,
- 10 medroxyprogesterone, budesonide, rimexolone, triamcinolone acetonide, fluticasone, mometasone furoate, methylprednisolone aceponate, cyclosporin A, tacrolimus, mycophenolate, ANA-245, immunosuppressive macrolide, methotrexate, PNP-405, MDL-74428, 9-(3,3-dimethyl-5-phosphonopentyl) guanine, DADMe-IMMG, CP-690,550, mycophenate, cyclosporin, and
- 15 mizoribine.

Compounds active against metabolic diseases include fluvastatin, pitavastatin, ospemifene, AGI-1067, lovastatin, cerivastatin, pravastatin, simvastatin, atorvastatin, sulfonylurea, troglitazone, rosiglitazone, pioglitazone, R-483, MK-767, tesagliptazar, and rosuvastatin.

- 20 Anti-cancer compounds include gefitinib, imatinib, erlotinib, vatalanib, fosteabine, camptosar, irinotecan, hycamtin, femara, letrozole, fadrozole, temozolamide, etopophos, anastrozole, arimidex, carboplatin, paraplatin, exemestane, atamestane, epirubicin, adriamycin, taxotere, taxol, vinorelbine, ospemifene, troglitazone, etoposide, everolimus, vincristine, sirolimus,
- 25 raltitrexed (tomudex), aminopterin, alvocidib, bortezomib, VX-148, vinblastine, tipifarnib, mitoxantrone, vindesine, lonafarib, merimepodib, brequinar, amsacrine, CEP-701, decitabine, teniposide, midostaurin, MLN-518, PD-184352, emetrexed (ALIMTA), 10-propargyl-10-deaza-aminopterin (PDX), tacedinaline, thalidomide, TLK-286, pixantrone, pentostatin, enocitabine,
- 30 clofarabine, BCX-1777, rubitecan, suberanilohydroxamic acid, revimid, MS-275, dexamethasone, LAQ-824, fludarabine, pirarubicin, teriflunomide, cerubidin HCL, idarubicin HCL, exatecan, sardomozide, adriamycin,

methopterin, mizoribine, tamoxifen citrate/toremifene citrate, raloxifene hydrochloride, mycophenolate, dexamethasone, methotrexate, GLEEVEC, PNP-405, MDL-74428, 9-(3,3-dimethyl-5-phosphonopentyl) guanine, DADMe-IMMG, camptosar, idarubicin, leflunomide, BAY-43-9006, bicyclo nucleobase compounds, 2-fluoro, 2', 3' didehydro, 4' phosphonate nucleoside compounds, gemcitabine, cladribine, rofecoxib, and halobetasol propionate.

5 Purine nucleoside phosphorylase inhibitors include BCX-1777, PNP-405, MDL-74428, 9-(3,3-dimethyl-5-phosphonopentyl) guanine, and DADMe-IMMG.

10 Kinase inhibitors include gefitinib, imatinib, erlotinib, vatalanib, alvocidib, CEP-701, GLEEVEC, midostaurin, MLN-518, PD-184352, doramapimod, BAY-43-9006, and CP-690,550.

15 Antimetabolites include raltitrexed (tomudex), aminopterin, pemetrexed (ALIMTA), 10-propargyl-10-deaza-aminopterin (PDX), methopterin and methotrexate.

IMPDH inhibitors include VX-148, merimepodib, mizoribine, and mycophenolate.

20 Nucleoside and nucleoside analogs include LY-582563, L-Fd4C, L-FddC, telbivudine, clevudine, dOTCP, dOTC, DDL DDLP, ddcP, ddC, DADP, DAPD, d4TP, D4T, 3TC, 3TCP FTCP, ABCP, AZT, IsoddAP, FTC, ribavirin, viramidine, L-enantiomers of ribavirin and viramidine, levovirin, ISODD A, D- and L-nucleosides, nucleosides, fosteabine, gemcitabine, cladribine, decitabine, entecavir, carbovir, abacavir, pentostatin, enocitabine, clofarabine, BCX-1777, ANA-245, and DADMe-IMMG.

25 Anti-infective compounds also include ethambutol, fluoroquinolones, rifabutin, rifampicin, erythromycin, isoniazid, pyrazinamid, and cefixime.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to, a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamide-ester group.

Typically, compounds of the invention have a molecular weight of from about 400 amu to about 10,000 amu; in a specific embodiment of the invention, compounds have a molecular weight of less than about 5000 amu; in another specific embodiment of the invention, compounds have a molecular weight of
5 less than about 2500 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 1000 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 800 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 600 amu; and in another
10 specific embodiment of the invention, compounds have a molecular weight of less than about 600 amu and a molecular weight of greater than about 400 amu.

The compounds of the invention also typically have a logD(polarity) less than about 5. In one embodiment the invention provides compounds having a logD less than about 4; in another one embodiment the invention provides
15 compounds having a logD less than about 3; in another one embodiment the invention provides compounds having a logD greater than about -5; in another one embodiment the invention provides compounds having a logD greater than about -3; and in another one embodiment the invention provides compounds having a logD greater than about 0 and less than about 3.

20 Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. For example, R^x contains a R^y substituent. R^y can be R², which in turn
25 can be R³. If R³ is selected to be R^{3c}, then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log
30 P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

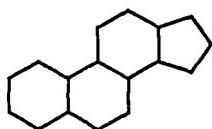
By way of example and not limitation, W^3 , R^y and R^3 are all recursive substituents in certain claims. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given claim. More typically, each of these may independently occur 12 or fewer 5 times in a given claim. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a given claim. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given claim.

Recursive substituents are an intended aspect of the invention. One of 10 ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an claim of the invention, the total number will be determined as set forth above.

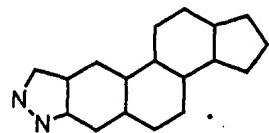
Whenever a compound described herein is substituted with more than 15 one of the same designated group, *e.g.*, “ R^1 ” or “ R^{6a} ”, then it will be understood that the groups may be the same or different, *i.e.*, each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

In one specific embodiment of the invention, the therapeutic compound is a non-steroidal anti-inflammatory compound.

20 In another specific embodiment of the invention, the therapeutic compound is a steroidal anti-inflammatory compound. Steroidal anti-inflammatories include those compounds that include the following fused ring system:



25 In one embodiment of the invention, the therapeutic compound is a steroidal anti-inflammatory compound that includes the following fused ring system:



In one embodiment of the invention, the compound is in an isolated and purified form. Generally, the term "isolated and purified" means that the compound is substantially free from biological materials (e.g. blood, tissue, cells, etc.). In one specific embodiment of the invention, the term means that the compound or conjugate of the invention is at least about 50 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 75 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 90 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 98 wt.% free from biological materials; and in another embodiment, the term means that the compound or conjugate of the invention is at least about 99 wt.% free from biological materials. In another specific embodiment, the invention provides a compound or conjugate of the invention that has been synthetically prepared (e.g., ex vivo).

In one embodiment of the invention, the compound is not an anti-inflammatory compound; in one embodiment, the compound is not a purine nucleoside phosphorylase inhibitor; in one embodiment the compound is not an anti-cancer compound; in one embodiment the compound is not active against immune-mediated conditions; in one embodiment the compound is not active against metabolic diseases; in one embodiment the compound is not an antiviral compound; in one embodiment the compound is not a nucleoside or nucleoside analog; in one embodiment the compound is not a kinase inhibitor; in one embodiment the compound is not an antimetabolite; in one embodiment the compound is not an IMPDH inhibitor; and in one embodiment the compound is not an anti-infective compound.

Stereoisomers

The compounds of the invention may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, *e.g.*, acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

25 Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+ , Li^+ , K^+ , Ca^{+2} and Mg^{+2} . Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+ , Na^+ , and K^+ . A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable
5 metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl , HBr , H_2SO_4 , H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in
10 their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids
15 found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Pharmaceutical Formulations

20 The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will
25 optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily
30 about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The

formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other 5 ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy.

10 Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with 15 liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or 20 granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a 25 suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and 30 optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For administration to the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in

5 increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

10 If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which
15 enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise
20 merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the
25 so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl
30 alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a

non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl

5 palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

10 Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When
15 used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more
20 agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium
25 carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by
30 known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action

over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example 5 calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions.

- 10 Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., 15 polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl 20 p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a 25 thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

- 30 Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and

suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain

approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For 5 example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 µg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, 10 especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose 15 and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

20 Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the 25 alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

30 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which 5 may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous 10 injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly 15 mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier 20 therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, 25 parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided compositions comprising one or more compounds of the 30 invention formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used

prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

10

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and 15 sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

20

Combination Therapy

Active ingredients of the invention can also be used in combination with other active ingredients. Such combinations are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties 25 of the combination. For example, when treating inflammation the compositions of the invention can be combined with other anti-inflammatory compounds.

It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be 30 administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

The combination therapy may provide "synergy" or a "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, *e.g.*, in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic therapeutic effect denotes a therapeutic effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes.

Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g., C¹⁴ or H³) compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no therapeutic activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37 °C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compounds of the invention. The compounds are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However,

- 5 many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as
10 March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

15 Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

- Generally, the reaction conditions such as temperature, reaction time,
20 solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically
25 consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

- Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20 °C), although for metal hydride
30 reductions frequently the temperature is reduced to 0 °C to -100 °C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0 °C to -100 °C) are also common.

Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and will be applied when applicable.

The terms “treated”, “treating”, “treatment”, and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that “treating compound one with compound two” is synonymous with “allowing compound one to react with compound two”, “contacting compound one with compound two”, “reacting compound one with compound two”, and other expressions common in the art of organic synthesis for reasonably indicating that compound one was “treated”, “reacted”, “allowed to react”, etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100 °C to 250 °C, typically -78 °C to 150 °C, more typically -78 °C to 100 °C, still more typically 0 °C to 100 °C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for “treating” in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes and in the examples (hereafter “exemplary schemes”) leads to various analogs of the specific

exemplary materials produce. The above-cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography.

Chromatography can involve any number of methods including, for example:

reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw

Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, 5 (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of 10 enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl- β -phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of 15 amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with 20 one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as 25 menthol derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthol ester, e.g., (-) 30 menthol chloroformate in the presence of base, or Mosher ester, α -methoxy- α -(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds 35 can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two

enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other 5 chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

Therapeutic Activity

Compositions of the invention are screened for therapeutic activity by 10 any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for therapeutic activity *in vitro* and compositions showing therapeutic activity are then screened for activity *in vivo*. Compositions having *in vitro* K_i (inhibitory constants) of less than about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably 15 less than about 5×10^{-8} M are preferred for *in vivo* use.

For example, the therapeutic properties of the compounds of the invention can be assessed using assays available to the art worker.

Examples General Section

20 A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples hereinbelow. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods. Certain compounds of the invention can be used as intermediates for the preparation of other compounds of 25 the invention. For example, the interconversion of various phosphonate compounds of the invention is illustrated below.

Interconversions of the Phosphonates R-LINK-P(O)(OR¹)₂, R-LINK-P(O)(OR¹)(OH) and R-LINK-P(O)(OH)₂.

30 The following schemes 32-38 described the preparation of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹ may be the same or different. The R¹ groups attached to a phosphonate ester, or to

precursors thereto, may be changed using established chemical transformations. The interconversion reactions of phosphonates are illustrated in Scheme S32. The group R in Scheme 32 represents the substructure, *i.e.* the drug “scaffold, to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds of the invention, or in precursors thereto. At the point in the synthetic route of conducting a phosphonate interconversion, certain functional groups in R may be protected. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹, and of the substrate to which the phosphonate group is attached. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor. For example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, et al, (1992) *J. Med Chem.* 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, et al, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorus oxychloride (Patois, et al, (1990) *J. Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated *in situ* from corresponding cyclic phosphites (Silverburg, et al., (1996) *Tetrahedron lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphoroflouridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe et al., (1988) *Tetrahedron lett.*, 29:5763-66).

Phosphonate prodrugs of the present invention may also be prepared from the free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.* 57:6331), and other acid coupling reagents

including, but not limited to, carbodiimides (Alexander, et al, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara et al, (1992) *Bioorg. Med. Chem. Lett.* 2:145; Ohashi et al, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne et al 5 (1993) *Tetrahedron Lett.* 34:6743).

Aryl halides undergo Ni⁺² catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, et al (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic 10 triflates (Petrakis et al (1987) *J. Am. Chem. Soc.* 109:2831; Lu et al (1987) *Synthesis* 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel et al (1991) *Synthesis*, 691). N-Alkoxy aryl 15 salts with alkali metal derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also be extended to compounds where the W⁵ group is a heterocycle. Cyclic-1,3-propenyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted 20 propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (e.g., pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The conversion of a phosphonate diester S32.1 into the corresponding 25 phosphonate monoester S32.2 (Scheme 32, Reaction 1) is accomplished by a number of methods. For example, the ester S32.1 in which R¹ is an aralkyl group such as benzyl, is converted into the monoester compound S32.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.* (1995) 60:2946. The reaction is 30 performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110 °C. The conversion of the diester S32.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester S32.2 is effected by

treatment of the ester S32.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters S32.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, is converted into the monoesters S32.2 in which R¹ is alkyl by 5 hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, is converted into the monoester S32.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using 10 the procedure described in *J. Org. Chem.* (1973) 38:3224, for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester S32.1 or a phosphonate monoester S32.2 into the corresponding phosphonic acid S32.3 (Scheme 32, Reactions 2 and 3) can be effected by reaction of the diester or the monoester 15 with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, (1979) 739. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester S32.2 in which R¹ is aralkyl such as benzyl, is converted into the 20 corresponding phosphonic acid S32.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester S32.2 in which R¹ is alkenyl such as, for example, allyl, is converted into the phosphonic acid S32.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous 25 dioxane, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.* (1985) 68:618. Palladium catalyzed hydrogenolysis of phosphonate esters S32.1 in which R¹ is benzyl is described in *J. Org. Chem.* (1959) 24:434. Platinum-catalyzed hydrogenolysis of phosphonate esters S32.1 in which R¹ is phenyl is described in *J. Am. Chem. Soc.* (1956) 78:2336.

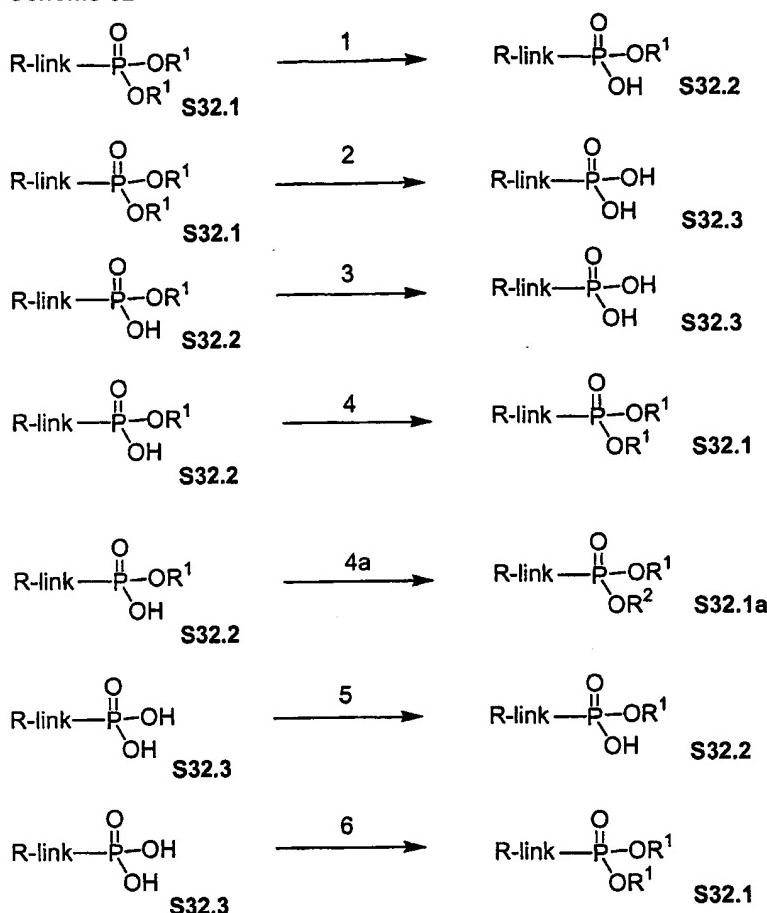
30 The conversion of a phosphonate monoester S32.2 into a phosphonate diester S32.1 (Scheme 32, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number

of reactions in which the substrate S32.2 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Typically, the second phosphonate ester group is different than the first introduced phosphonate ester group, *i.e.* R¹ is followed by the introduction of R² where each of R¹ and R² is alkyl, aralkyl,
5 haloalkyl such as chloroethyl, or aralkyl (Scheme 32, Reaction 4a) whereby S32.2 is converted to S32.1a. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tritylolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in
10 which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrichiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester S32.2 to the diester S32.1 is effected by the use of the
15 Mitsunobu reaction, as described above (Scheme 7). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester S32.2 is transformed into the phosphonate diester S32.1,
20 in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium
25 carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester S32.2 is transformed into the chloro analog RP(O)(OR¹)Cl by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976,
30 p. 17, and the thus-obtained product RP(O)(OR¹)Cl is then reacted with the hydroxy compound R¹OH, in the presence of a base such as triethylamine, to afford the phosphonate diester S32.1.

A phosphonic acid R-link-P(O)(OH)₂ is transformed into a phosphonate monoester RP(O)(OR¹)(OH) (Scheme 32, Reaction 5) by means of the methods described above for the preparation of the phosphonate diester R-link-P(O)(OR¹)₂ S32.1, except that only one molar proportion of the component 5 R¹OH or R¹Br is employed. Dialkyl phosphonates may be prepared according to the methods of: Quast et al (1974) *Synthesis* 490; Stowell et al (1990) *Tetrahedron Lett.* 3261; US 5663159.

A phosphonic acid R-link-P(O)(OH)₂ S32.3 is transformed into a phosphonate diester R-link-P(O)(OR¹)₂ S32.1 (Scheme 32, Reaction 6) by a 10 coupling reaction with the hydroxy compound R¹OH, in the presence of a coupling agent such as Aldri thiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids S32.3 are transformed into phosphonic esters S32.1 in which R¹ is aryl, by means of a coupling reaction employing, for example, 15 dicyclohexylcarbodiimide in pyridine at ca 70 °C. Alternatively, phosphonic acids S32.3 are transformed into phosphonic esters S32.1 in which R¹ is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R¹Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the 20 phosphonic ester S32.1.

Scheme 32

Preparation of phosphonate carbamates.

Phosphonate esters may contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff. The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US 6018049.

Scheme 33 illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme 33, in the general reaction generating carbamates, an alcohol S33.1, is converted into the activated derivative S33.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like,

as described herein. The activated derivative S33.2 is then reacted with an amine S33.3, to afford the carbamate product S33.4. Examples 1 – 7 in Scheme 33 depict methods by which the general reaction is effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

5 Scheme 33, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the alcohol S33.5. In this procedure, the alcohol S33.5 is reacted with phosgene, in an inert solvent such as toluene, at about 0 °C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate S33.6. The latter compound is then reacted with the amine component S33.3, in the presence of an organic or inorganic base, to afford the carbamate S33.7. For example, the chloroformyl compound S33.6 is reacted with the amine S33.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate S33.7. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

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Scheme 33, Example 2 depicts the reaction of the chloroformate compound S33.6 with imidazole to produce the imidazolide S33.8. The imidazolide product is then reacted with the amine S33.3 to yield the carbamate S33.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in *J. Med. Chem.*, 1989, 32, 357.

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Scheme 33 Example 3, depicts the reaction of the chloroformate S33.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester S33.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds S33.19 - S33.24 shown in Scheme 33, and similar compounds. For example, if the component R"OH is hydroxybenztriazole S33.19, N-

30

hydroxysuccinimide S33.20, or pentachlorophenol, S33.21, the mixed carbonate S33.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in *Can. J. Chem.*, 1982, 60, 976. A similar reaction in which the 5 component R"OH is pentafluorophenol S33.22 or 2-hydroxypyridine S33.23 is performed in an ethereal solvent in the presence of triethylamine, as described in *Syn.*, 1986, 303, and *Chem. Ber.* 118, 468, 1985.

Scheme 33 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole S33.8 is employed. In this procedure, an alcohol 10 S33.5 is reacted with an equimolar amount of carbonyl diimidazole S33.11 to prepare the intermediate S33.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole S33.8 is then reacted with an equimolar amount of the amine R'NH₂ to afford the carbamate S33.7. The reaction is performed in an aprotic organic solvent such as 15 dichloromethane, as described in *Tet. Lett.*, 42, 2001, 5227, to afford the carbamate S33.7.

Scheme 33, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benztriazole S33.13. In this procedure, an alcohol ROH is reacted at ambient temperature with an equimolar amount of 20 benztriazole carbonyl chloride S33.12, to afford the alkoxy carbonyl product S33.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in *Synthesis.*, 1977, 704. The product is then reacted with the amine R'NH₂ to afford the carbamate S33.7. The reaction is conducted in toluene or 25 ethanol, at from ambient temperature to about 80 °C as described in *Synthesis.*, 1977, 704.

Scheme 33, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, S33.14, is reacted with an alcohol S33.5 to afford the intermediate alkyloxycarbonyl intermediate S33.15. The latter reagent is then 30 reacted with the amine R'NH₂ to afford the carbamate S33.7. The procedure in which the reagent S33.15 is derived from hydroxybenztriazole S33.19 is described in *Synthesis*, 1993, 908; the procedure in which the reagent S33.15 is

derived from N-hydroxysuccinimide **S33.20** is described in *Tet. Lett.*, 1992, 2781; the procedure in which the reagent **S33.15** is derived from 2-hydroxypyridine **S33.23** is described in *Tet. Lett.*, 1991, 4251; the procedure in which the reagent **S33.15** is derived from 4-nitrophenol **S33.24** is described in 5 *Synthesis*, 1993, 103. The reaction between equimolar amounts of the alcohol ROH and the carbonate **S33.14** is conducted in an inert organic solvent at ambient temperature.

10 Scheme 33, Example 7 illustrates the preparation of carbamates from alkoxy carbonyl azides **S33.16**. In this procedure, an alkyl chloroformate **S33.6** is reacted with an azide, for example sodium azide, to afford the alkoxy carbonyl azide **S33.16**. The latter compound is then reacted with an equimolar amount of the amine R'NH₂ to afford the carbamate **S33.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in *Synthesis*, 1982, 404.

15 Scheme 33, Example 8 illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and the chloroformyl derivative of an amine **S33.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the 20 presence of a base such as triethylamine, to afford the carbamate **S33.7**.

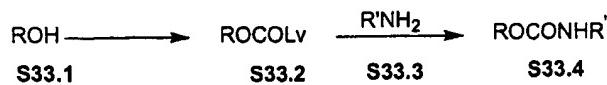
25 Scheme 33, Example 9 illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and an isocyanate **S33.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **S33.7**.

30 Scheme 33, Example 10 illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and an amine R'NH₂. In this procedure, which is described in *Chem. Lett.* 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and

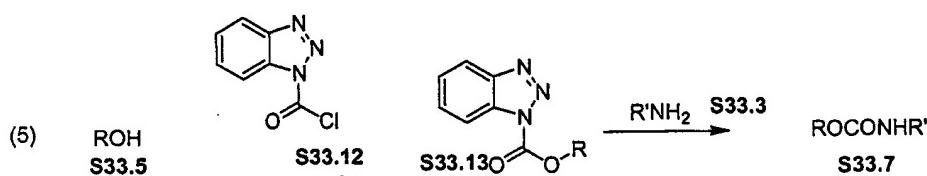
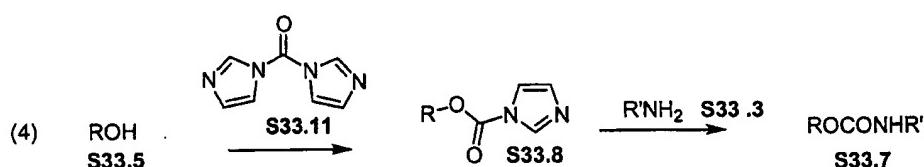
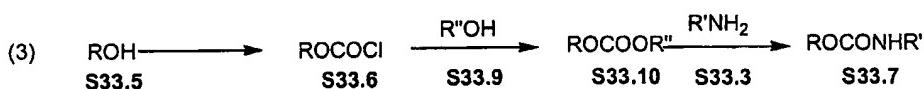
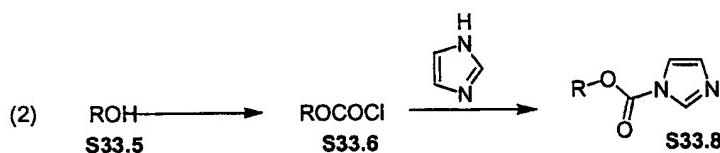
selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate S33.7.

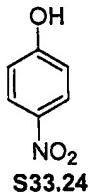
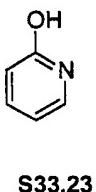
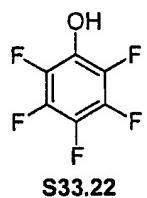
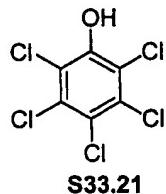
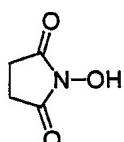
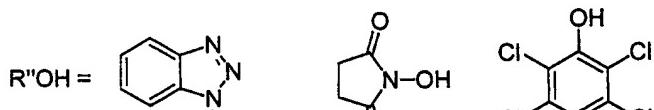
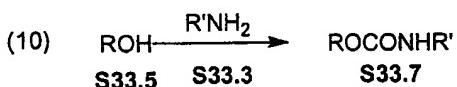
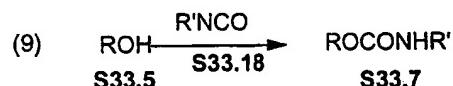
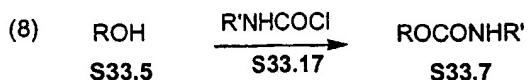
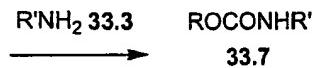
Scheme 33. Preparation of carbamates.

General reaction



Examples





Preparation of Carboalkoxy-substituted Phosphonate Bisamidates,

Monoamidates, Diesters and Monoesters.

5 A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is

either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is
5 accomplished by reaction with thionyl chloride, for example as described in *J. Gen. Chem. USSR*, 1983, 53, 480, *Zh. Obschei Khim.*, 1958, 28, 1063, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with oxalyl chloride, as described in *J. Am. Chem. Soc.*, 1994, 116, 3251, or *J. Org. Chem.*, 1994, 59, 6144, or by
reaction with phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66,
10 329, or in *J. Med. Chem.*, 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amide or ester products.

Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in *J. Chem. Soc., Chem. Comm.*
15 (1991) 312, or *Nucleosides & Nucleotides* (2000) 19:1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride or with triisopropylbenzenesulfonyl chloride, as described in *Tet. Lett.* (1996) 7857, or *Bioorg. Med. Chem. Lett.* (1998) 8:663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy
20 compounds to afford amides or esters.

Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amides and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in *J. Chem. Soc., Chem. Comm.* (1991) 312 or *Coll. Czech. Chem. Comm.* (1987) 52:2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in *Tet. Lett.*, (2001) 42:8841, or *Nucleosides & Nucleotides* (2000) 19:1885.

A number of additional coupling reagents have been described for the
30 preparation of amides and esters from phosphonic acids. The agents include Aldrichiol-2, and PYBOP and BOP, as described in *J. Org. Chem.*, 1995, 60, 5214, and *J. Med. Chem.* (1997) 40:3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-

triazole (MSNT), as described in *J. Med. Chem.* (1996) 39:4958, diphenylphosphoryl azide, as described in *J. Org. Chem.* (1984) 49:1158, 1-(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in *Bioorg. Med. Chem. Lett.* (1998) 8:1013,
5 bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in *Tet. Lett.*, (1996) 37:3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane, as described in *Nucleosides Nucleotides* 1995, 14, 871, and diphenyl chlorophosphate, as described in *J. Med. Chem.*, 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the
10 Mitsunobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in *Org. Lett.*, 2001, 3, 643, or *J. Med. Chem.*, 1997, 40, 3842.

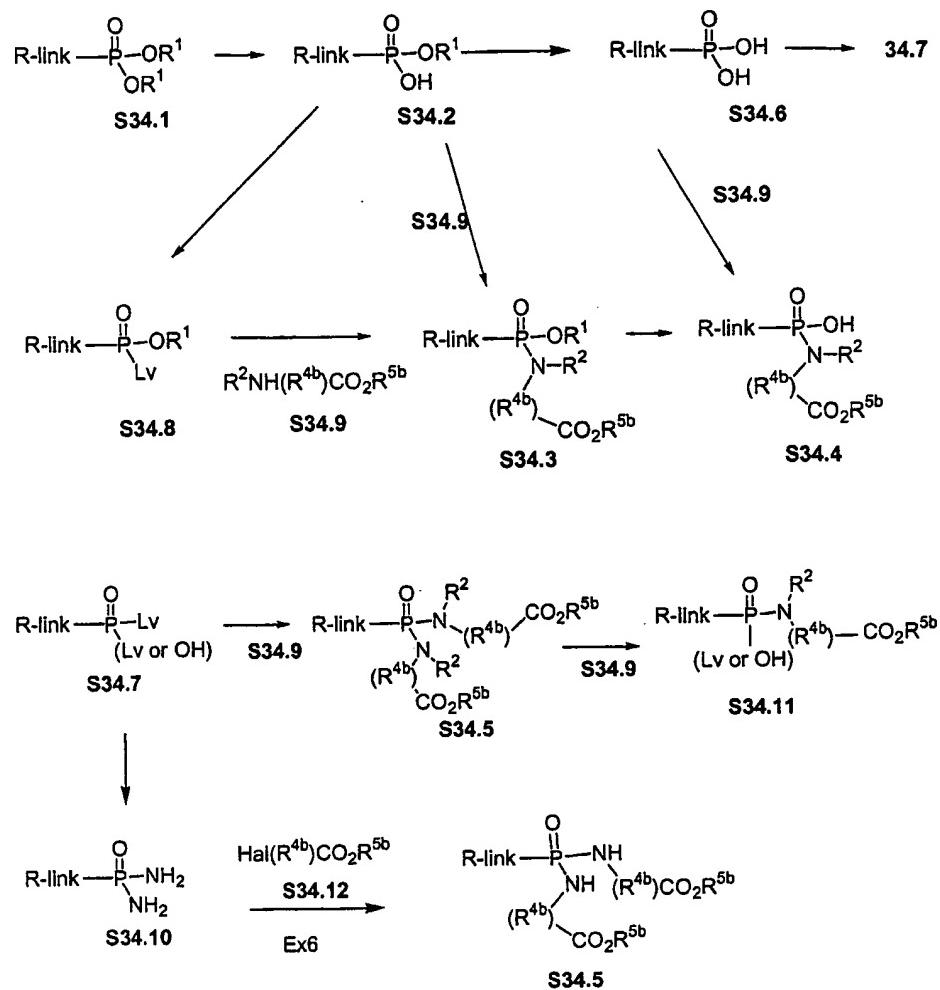
Phosphonic esters are also obtained by the reaction between phosphonic
15 acids and halo compounds, in the presence of a suitable base. The method is described, for example, in *Anal. Chem.*, 1987, 59, 1056, or *J. Chem. Soc. Perkin Trans., I*, 1993, 19, 2303, or *J. Med. Chem.*, 1995, 38, 1372, or *Tet. Lett.*, 2002, 43, 1161.

Schemes 34-37 illustrate the conversion of phosphonate esters and
20 phosphonic acids into carboalkoxy-substituted phosphonbisamidates (Scheme 34), phosphonamidates (Scheme 35), phosphonate monoesters (Scheme 36) and phosphonate diesters, (Scheme 37). Scheme 38 illustrates synthesis of gem-dialkyl amino phosphonate reagents.

Scheme 34 illustrates various methods for the conversion of phosphonate
25 diesters S34.1 into phosphonbisamidates S34.5. The diester S34.1, prepared as described previously, is hydrolyzed, either to the monoester S34.2 or to the phosphonic acid S34.6. The methods employed for these transformations are described above. The monoester S34.2 is converted into the monoamide S34.3 by reaction with an aminoester S34.9, in which the group R² is H or alkyl; the
30 group R^{4b} is a divalent alkylene moiety such as, for example, CHCH₃, CHCH₂CH₃, CH(CH(CH₃)₂), CH(CH₂Ph), and the like, or a side chain group present in natural or modified aminoacids; and the group R^{5b} is C₁-C₁₂ alkyl,

such as methyl, ethyl, propyl, isopropyl, or isobutyl; C₆–C₂₀ aryl, such as phenyl or substituted phenyl; or C₆–C₂₀ arylalkyl, such as benzyl or benzhydryl. The reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in *J. Am. Chem. Soc.*, (1957) 79:3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amide product S34.3. The amide-forming reaction is also effected in the presence of coupling agents such as BOP, as described in *J. Org. Chem.* (1995) 60:5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants S34.2 and S34.9 are transformed into the monoamidate S34.3 by means of a Mitsunobu reaction. The preparation of amides by means of the Mitsunobu reaction is described in *J. Med. Chem.* (1995) 38:2742. Equimolar amounts of the reactants are combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester S34.3 is then transformed into amidate phosphonic acid S34.4. The conditions used for the hydrolysis reaction depend on the nature of the R¹ group, as described previously. The phosphonic acid amide S34.4 is then reacted with an aminoester S34.9, as described above, to yield the bisamide product S34.5, in which the amino substituents are the same or different. Alternatively, the phosphonic acid S34.6 may be treated with two different amino ester reagents simultaneously, i.e. S34.9 where R², R^{4b} or R^{5b} are different. The resulting mixture of bisamide products S34.5 may then be separable, e.g. by chromatography.

Scheme 34



5

An example of this procedure is shown in Scheme 34, Example 1. In this procedure, a dibenzyl phosphonate S34.14 is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as described in *J. Org. Chem.*, 1995, 60, 2946, to afford the monobenzyl phosphonate S34.15. The product is then reacted with equimolar amounts of ethyl alaninate S34.16 and dicyclohexyl carbodiimide in pyridine, to yield the amidate product S34.17. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product S34.18 which may be unstable according to *J. Med. Chem.* (1997) 40(23):3842. This compound S34.18 is then reacted in a Mitsunobu reaction with ethyl leucinate S34.19, triphenyl phosphine and

diethylazodicarboxylate, as described in *J. Med. Chem.*, 1995, 38, 2742, to produce the bisamide product S34.20.

Using the above procedures, but employing in place of ethyl leucinate S34.19 or ethyl alaninate S34.16, different aminoesters S34.9, the corresponding 5 products S34.5 are obtained.

Alternatively, the phosphonic acid S34.6 is converted into the bisamide S34.5 by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product S34.5 are the same, or in two steps, in which case the nitrogen-10 related substituents can be different.

An example of the method is shown in Scheme 34, Example 2. In this procedure, a phosphonic acid S34.6 is reacted in pyridine solution with excess ethyl phenylalaninate S34.21 and dicyclohexylcarbodiimide, for example as described in *J. Chem. Soc., Chem. Comm.*, 1991, 1063, to give the bisamide product S34.22.
15

Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters S34.9, the corresponding products S34.5 are obtained.

As a further alternative, the phosphonic acid S34.6 is converted into the 20 mono or bis-activated derivative S34.7, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides S34.7 (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17.
25 The conversion of phosphonic acids into monoimidazolides S34.7 (Lv = imidazolyl) is described in *J. Med. Chem.*, 2002, 45, 1284 and in *J. Chem. Soc. Chem. Comm.*, 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in *Nucleosides and Nucleotides*, 2000, 10, 1885. The activated product is then reacted with the 30 aminoester S34.9, in the presence of a base, to give the bisamide S34.5. The reaction is performed in one step, in which case the nitrogen substituents present

in the product S34.5 are the same, or in two steps, via the intermediate S34.11, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme 34, Examples 3 and 5.

In the procedure illustrated in Scheme 34, Example 3, a phosphonic acid S34.6 is 5 reacted with ten molar equivalents of thionyl chloride, as described in *Zh.*

Obschei Khim., 1958, 28, 1063, to give the dichloro compound S34.23. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate S34.24 to afford the bisamide product S34.25.

10 Using the above procedures, but employing, in place of butyl serinate S34.24, different aminoesters S34.9, the corresponding products S34.5 are obtained.

15 In the procedure illustrated in Scheme 34, Example 5, the phosphonic acid S34.6 is reacted, as described in *J. Chem. Soc. Chem. Comm.*, 1991, 312, with carbonyl diimidazole to give the imidazolide S34.S32. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate S34.33 to yield the monodisplacement product S34.S34. The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate S34.35, and the product is then reacted, under 20 the same conditions, with ethyl N-methylalaninate S34.33a to give the bisamide product S34.36.

Using the above procedures, but employing, in place of ethyl alaninate S34.33 or ethyl N-methylalaninate S34.33a, different aminoesters S34.9, the corresponding products S34.5 are obtained.

25 The intermediate monoamide S34.3 is also prepared from the monoester S34.2 by first converting the monoester into the activated derivative S34.8 in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product S34.8 is then reacted with an aminoester S34.9 in the presence of a base such as pyridine, to give an 30 intermediate monoamide product S34.3. The latter compound is then converted, by removal of the R¹ group and coupling of the product with the aminoester S34.9, as described above, into the bisamide S34.5.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative S34.26, is shown in Scheme 34, Example 4. In this procedure, the phosphonic monobenzyl ester S34.15 is reacted, in dichloromethane, with thionyl chloride, as described in *Tet. Letters.*, 1994, 35, 5 4097, to afford the phosphoryl chloride S34.26. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate S34.27 to yield the monoamidate product S34.28. The latter compound is hydrogenated in ethylacetate over a 5% palladium on carbon catalyst to produce the monoacid product S34.29. The product is 10 subjected to a Mitsunobu coupling procedure, with equimolar amounts of butyl alaninate S34.30, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamide product S34.31.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate S34.27 or butyl alaninate S34.30, different aminoesters S34.9, 15 the corresponding products S34.5 are obtained.

The activated phosphonic acid derivative S34.7 is also converted into the bisamide S34.5 via the diamino compound S34.10. The conversion of activated phosphonic acid derivatives such as phosphoryl chlorides into the corresponding amino analogs S34.10, by reaction with ammonia, is described in 20 Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The bisamino compound S34.10 is then reacted at elevated temperature with a haloester S34.12 (Hal = halogen, *i.e.* F, Cl, Br, I), in a polar organic solvent such as dimethylformamide, in the presence of a base such as 4, 4-dimethylaminopyridine (DMAP) or potassium carbonate, to yield the bisamide 25 S34.5. Alternatively, S34.6 may be treated with two different amino ester reagents simultaneously, *i.e.* S34.12 where R^{4b} or R^{5b} are different. The resulting mixture of bisamide products S34.5 may then be separable, *e.g.* by chromatography.

An example of this procedure is shown in Scheme 34, Example 6. In this 30 method, a dichlorophosphonate S34.23 is reacted with ammonia to afford the diamide S34.37. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is

then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate S34.38, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150 °C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamide product S34.39.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate S34.38, different haloesters S34.12 the corresponding products S34.5 are obtained.

The procedures shown in Scheme 34 are also applicable to the preparation of bisamides in which the aminoester moiety incorporates different functional groups. Scheme 34, Example 7 illustrates the preparation of bisamides derived from tyrosine. In this procedure, the monoimidazolidine S34.32 is reacted with propyl tyrosinate S34.40, as described in Example 5, to yield the monoamide S34.41. The product is reacted with carbonyl diimidazole to give the imidazolidine S34.42, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamide product S34.43.

Using the above procedures, but employing, in place of propyl tyrosinate S34.40, different aminoesters S34.9, the corresponding products S34.5 are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamides with the same or different amino substituents are prepared.

Scheme 35 illustrates methods for the preparation of phosphonate monoamides.

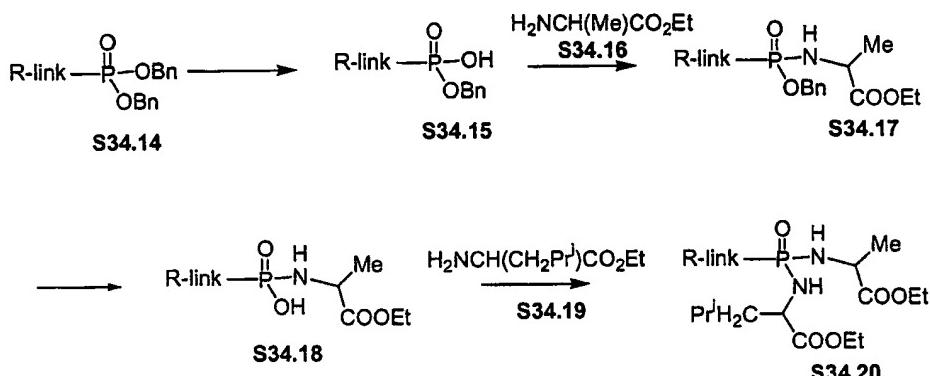
In one procedure, a phosphonate monoester S34.1 is converted, as described in Scheme 34, into the activated derivative S34.8. This compound is then reacted, as described above, with an aminoester S34.9, in the presence of a base, to afford the monoamide product S35.1.

The procedure is illustrated in Scheme 35, Example 1. In this method, a monophenyl phosphonate S35.7 is reacted with, for example, thionyl chloride, as described in *J. Gen. Chem. USSR.*, 1983, 32, 367, to give the chloro product S35.8. The product is then reacted, as described in Scheme 34, with ethyl alaninate S3, to yield the amide S35.10.

Using the above procedures, but employing, in place of ethyl alaninate S35.9, different aminoesters S34.9, the corresponding products S35.1 are obtained.

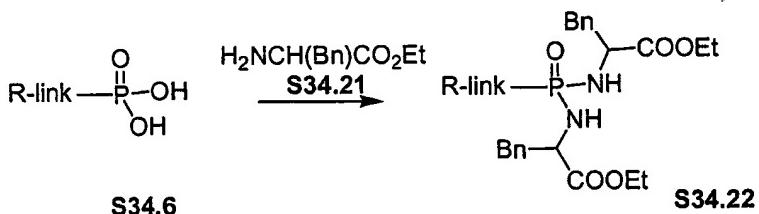
Alternatively, the phosphonate monoester S34.1 is coupled, as described in Scheme 34, with an aminoester S34.9 to produce the amidate S35.1. If necessary, the R¹ substituent is then altered, by initial cleavage to afford the phosphonic acid S35.2. The procedures for this transformation depend on the nature of the R¹ group, and are described above. The phosphonic acid is then transformed into the ester amidate product S35.3, by reaction with the hydroxy compound R³OH, in which the group R³ is aryl, heterocycle, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrichiol-2, PYBOP, Mitsunobu reaction etc) described in Scheme 34 for the coupling of amines and phosphonic acids.

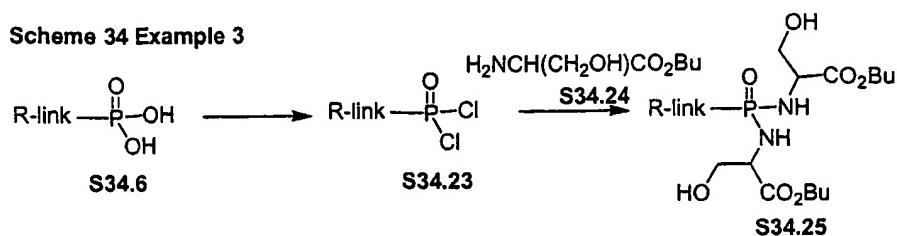
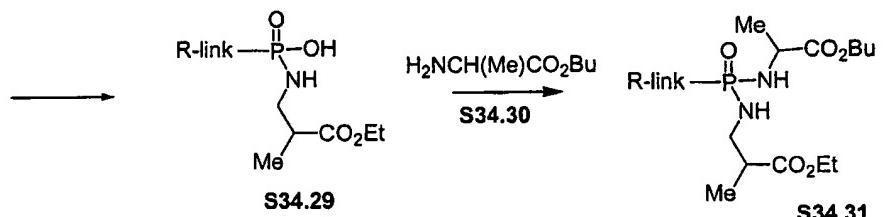
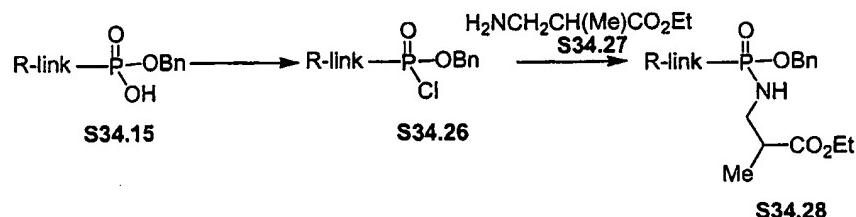
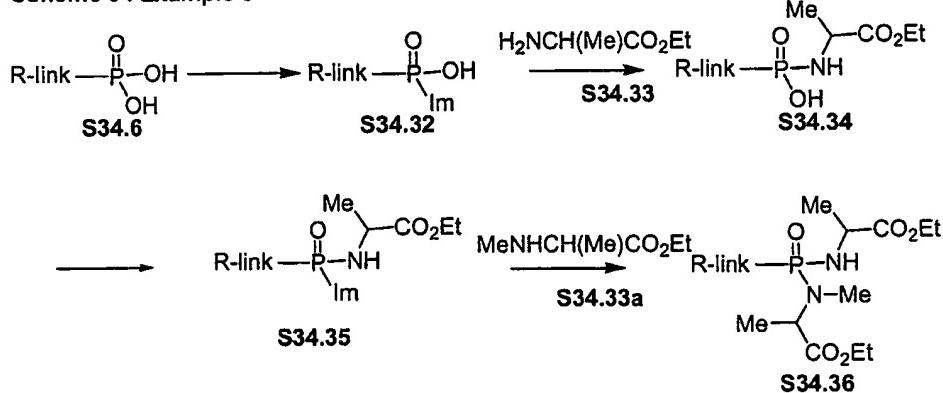
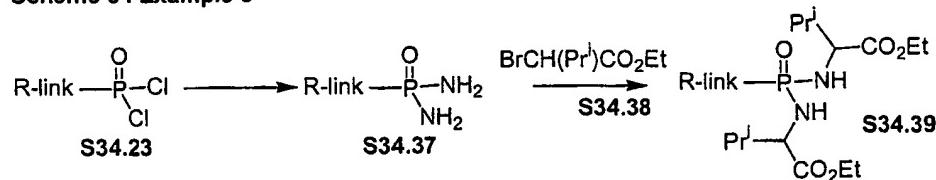
Scheme 34 Example 1

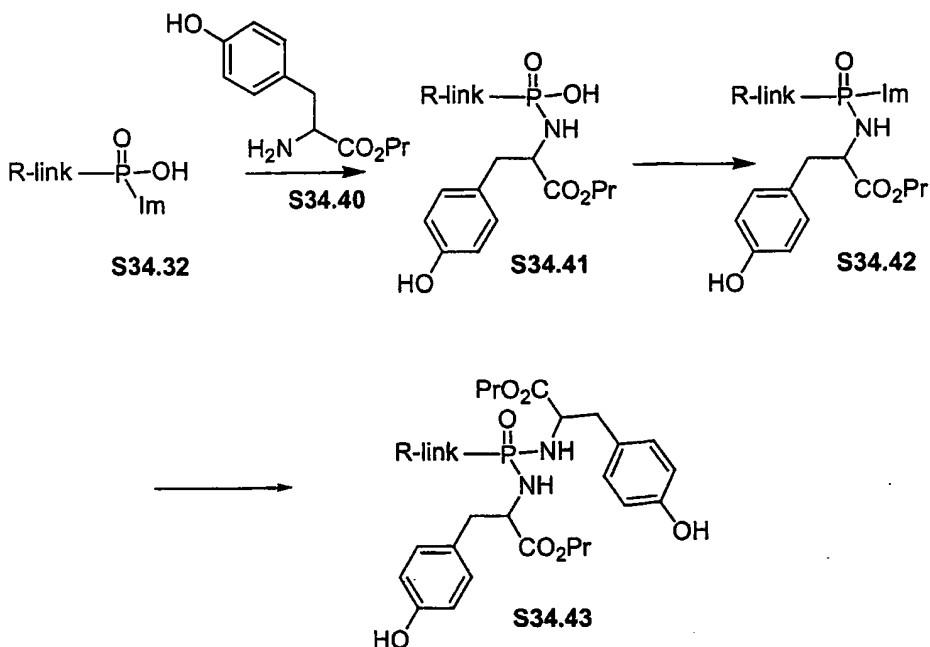


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Scheme 34 Example 2



Scheme 34 Example 3**Scheme 34 Example 4****Scheme 34 Example 5****Scheme 34 Example 6**

Scheme 34 Example 7

Examples of this method are shown in Scheme 35, Examples and 2 and 3. In the sequence shown in Example 2, a monobenzyl phosphonate S35.11 is 5 transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate S35.12. The benzyl group is then removed by catalytic hydrogenation in ethylacetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate S35.13. The product is then reacted in dichloromethane solution at ambient temperature with equimolar 10 amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol S35.14, for example as described in *Tet. Lett.*, 2001, 42, 8841, to yield the amidate ester S35.15.

In the sequence shown in Scheme 35, Example 3, the monoamidate S35.13 is coupled, in tetrahydrofuran solution at ambient temperature, with 15 equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine S35.16, to produce the amidate ester product S35.17.

Using the above procedures, but employing, in place of the ethyl alaninate product S35.12 different monoacids S35.2, and in place of

trifluoroethanol **S35.14** or 4-hydroxy-N-methylpiperidine **S35.16**, different hydroxy compounds R^3OH , the corresponding products **S35.3** are obtained.

Alternatively, the activated phosphonate ester **S34.8** is reacted with ammonia to yield the amide **S35.4**. The product is then reacted, as described in

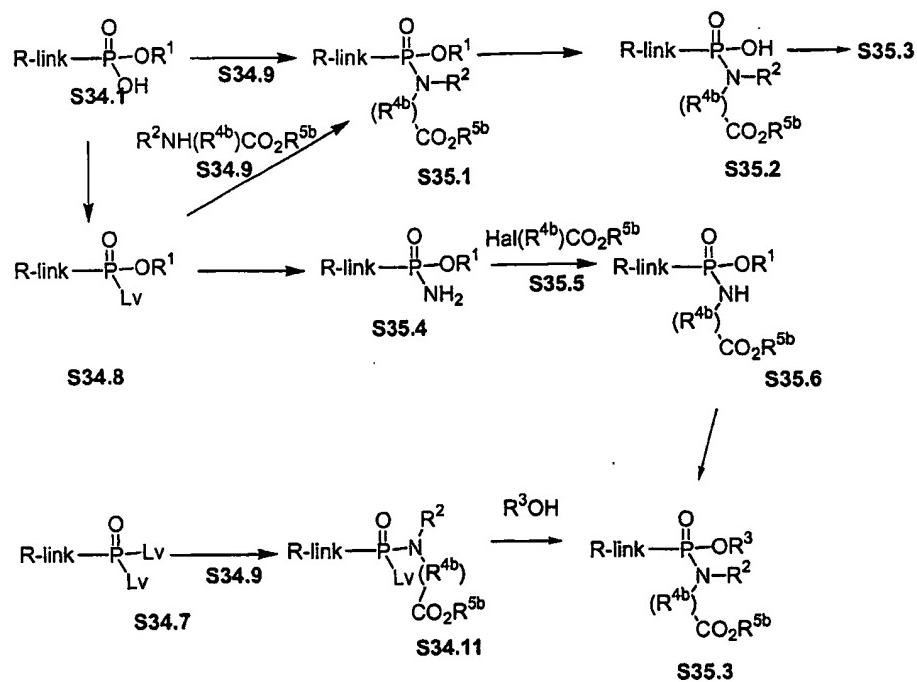
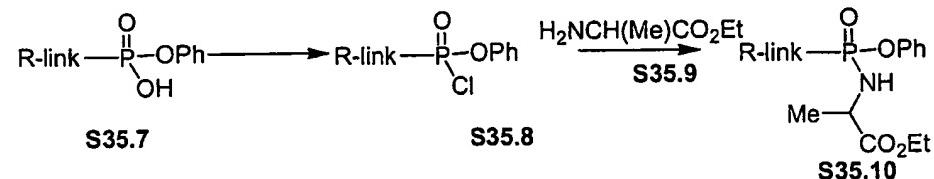
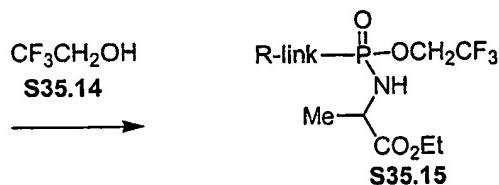
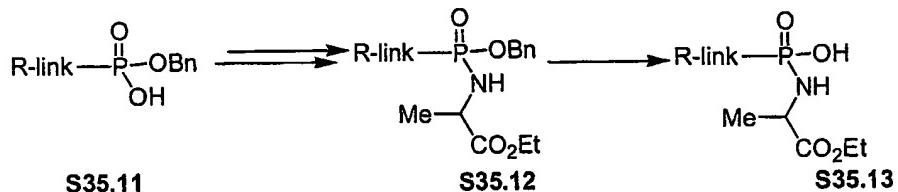
- 5 Scheme 34, with a haloester **S35.5**, in the presence of a base, to produce the amide product **S35.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **S35.3**. The method is illustrated in Scheme 35, Example 4. In this sequence, the monophenyl phosphoryl chloride **S35.18** is reacted, as described in Scheme 34, with
10 ammonia, to yield the amino product **S35.19**. This material is then reacted in N-methylpyrrolidinone solution at 170° with butyl 2-bromo-3-phenylpropionate **S35.20** and potassium carbonate, to afford the amide product **S35.21**.

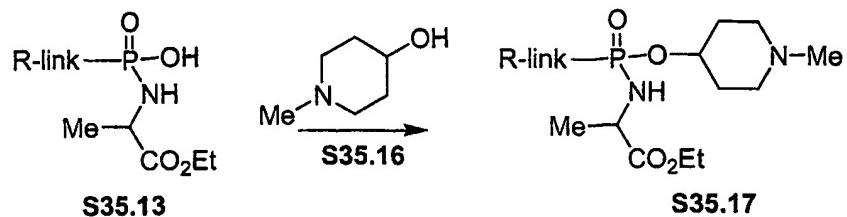
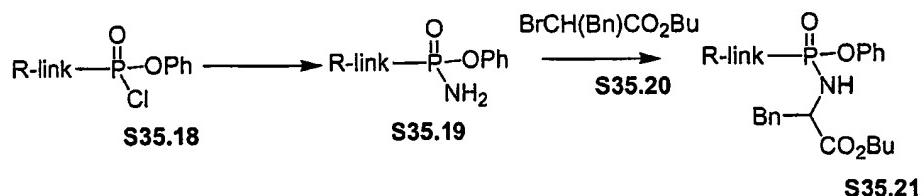
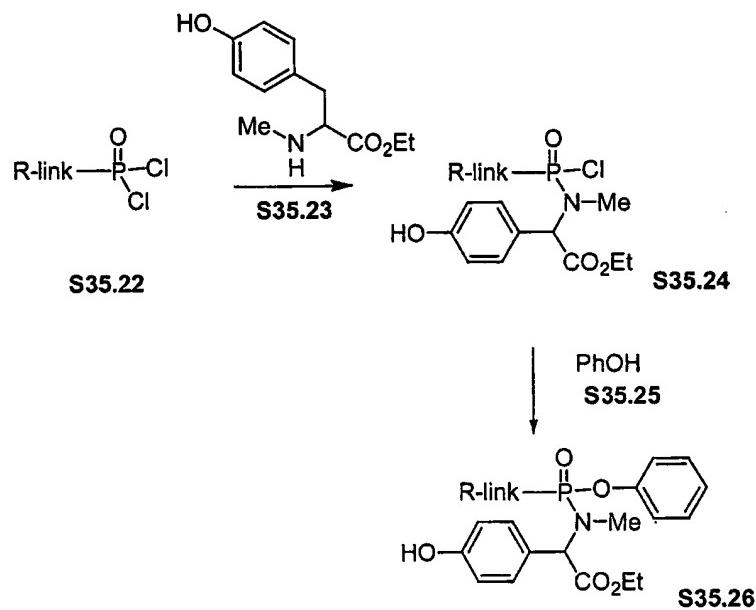
Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **S35.20**, different haloesters **S35.5**, the corresponding products
15 **S35.6** are obtained.

The monoamidate products **S35.3** are also prepared from the doubly activated phosphonate derivatives **S34.7**. In this procedure, examples of which are described in *Synlett.*, 1998, 1, 73, the intermediate **S34.7** is reacted with a limited amount of the aminoester **S34.9** to give the mono-displacement product
20 **S34.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **S35.3**.

The method is illustrated in Scheme 35, Example 5. In this method, the phosphoryl dichloride **S35.22** is reacted in dichloromethane solution with one
25 molar equivalent of ethyl N-methyl tyrosinate **S35.23** and dimethylaminopyridine, to generate the monoamidate **S35.24**. The product is then reacted with phenol **S35.25** in dimethylformamide containing potassium carbonate, to yield the ester amide product **S35.26**.

Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **S35.23** or phenol **S35.25**, the aminoesters **S34.9** and/or the hydroxy compounds R^3OH , the corresponding products **S35.3** are obtained.

Scheme 35**Scheme 35 Example 1****Scheme 35 Example 2**

Scheme 35 Example 3**Scheme 35 Example 4****Scheme 35 Example 5**

Scheme 36 illustrates methods for the preparation of carboalkoxy-
5 substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

In one procedure, a phosphonate monoester **S34.1**, prepared as described above, is coupled, using one of the methods described above, with a

hydroxyester S36.1, in which the groups R^{4b} and R^{5b} are as described in Scheme 34. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in *Aust. J. Chem.*, 1963, 609, optionally in the presence of dimethylaminopyridine, as described in *Tet.*, 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme 36, Example 1. In this method, a monophenyl phosphonate S36.9 is coupled, in dichloromethane solution in the presence of dicyclohexyl carbodiimide, with ethyl 3-hydroxy-2-methylpropionate S36.10 to yield the phosphonate mixed diester S36.11.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate S36.10, different hydroxyesters S33.1, the corresponding products S33.2 are obtained.

The conversion of a phosphonate monoester S34.1 into a mixed diester S36.2 is also accomplished by means of a Mitsunobu coupling reaction with the hydroxyester S36.1, as described in *Org. Lett.*, 2001, 643. In this method, the reactants S34.1 and S36.1 are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester S36.2. The R¹ substituent is varied by cleavage, using the methods described previously, to afford the monoacid product S36.3. The product is then coupled, for example using methods described above, with the hydroxy compound R³OH, to give the diester product S36.4.

The procedure is illustrated in Scheme 36, Example 2. In this method, a monoallyl phosphonate S36.12 is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate S36.13 to give the mixed diester S36.14. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product S36.15. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine S36.16 to yield the mixed diester S36.17.

Using the above procedures, but employing, in place of the ethyl lactate S36.13 or 3-hydroxypyridine, a different hydroxyester S36.1 and/or a different hydroxy compound R³OH, the corresponding products S36.4 are obtained.

The mixed diesters S36.2 are also obtained from the monoesters S34.1
5 via the intermediacy of the activated monoesters S36.5. In this procedure, the monoester S34.1 is converted into the activated compound S36.5 by reaction with, for example, phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in *Nucleosides and Nucleotides*, 2000, 19, 1885, or with carbonyl diimidazole, as described in *J. Med. Chem.*, 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester S36.1, as described above, to yield the mixed diester S36.2.

The procedure is illustrated in Scheme 36, Example 3. In this sequence, a
15 monophenyl phosphonate S36.9 is reacted, in acetonitrile solution at 70 °C, with ten equivalents of thionyl chloride, so as to produce the phosphoryl chloride S36.19. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate S36.20 in dichloromethane containing triethylamine, to give the mixed diester S36.21.

20 Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate S36.20, different hydroxyesters S36.1, the corresponding products S36.2 are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R³O group into intermediates S36.3 in which the
25 hydroxyester moiety is already incorporated. In this procedure, the monoacid intermediate S36.3 is converted into the activated derivative S36.6 in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R³OH, in the presence of a base, to yield the mixed diester product
30 S36.4.

The method is illustrated in Scheme 36, Example 4. In this sequence, the phosphonate monoacid S36.22 is reacted with trichloromethanesulfonyl chloride

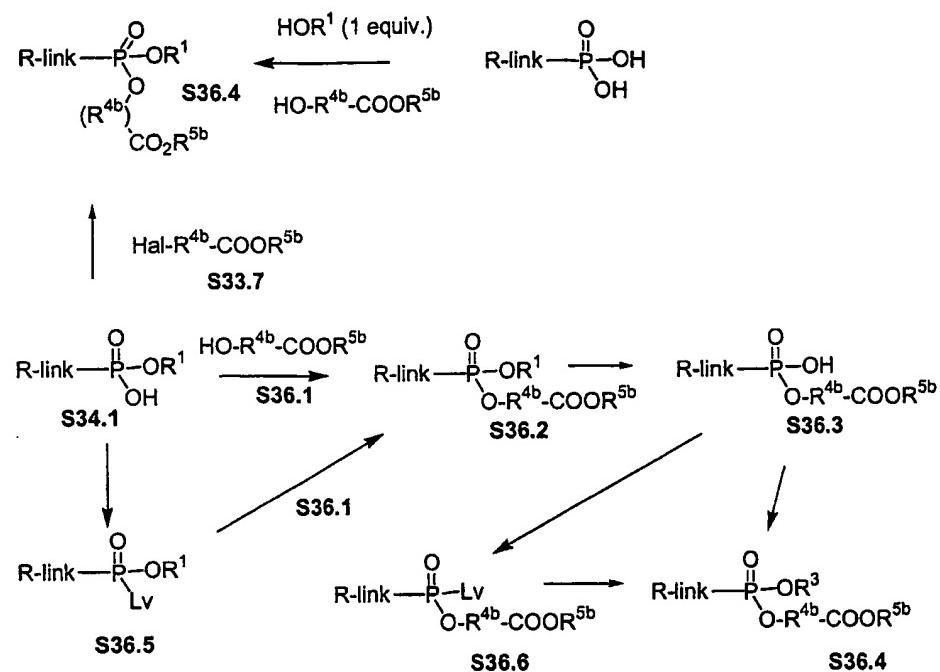
in tetrahydrofuran containing collidine, as described in *J. Med. Chem.*, 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **S36.23**. This compound is reacted with 3-(morpholinomethyl)phenol **S36.24** in dichloromethane containing triethylamine, to yield the mixed diester product
5 **S36.25**.

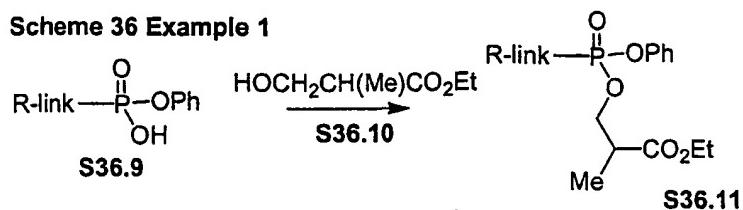
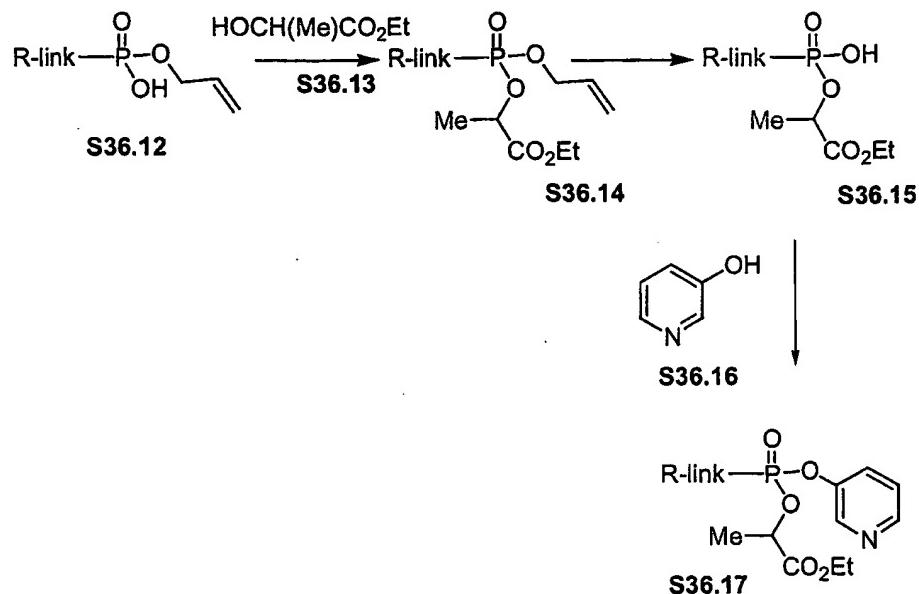
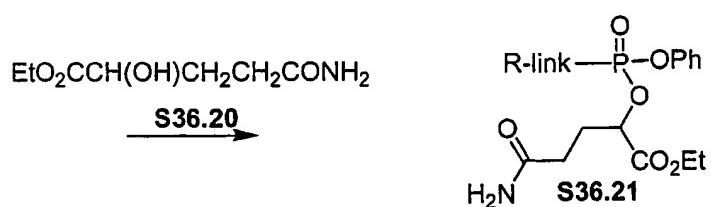
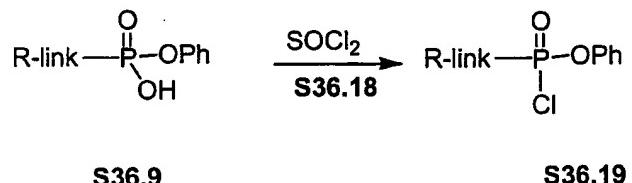
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **S36.24**, different alcohols R^3OH , the corresponding products **S36.4** are obtained.

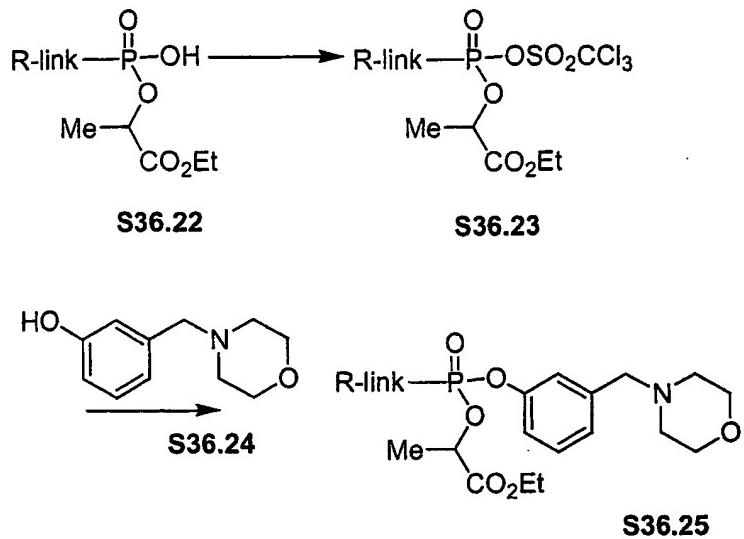
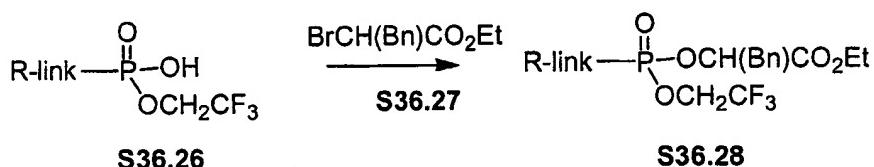
The phosphonate esters **S36.4** are also obtained by means of alkylation reactions performed on the monoesters **S34.1**. The reaction between the monoacid **S34.1** and the haloester **S36.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in *Anal. Chem.*, 1987, 59, 1056, or triethylamine, as described in *J. Med. Chem.*, 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as described in *Syn. Comm.*, 1995, 25, 3565.

The method is illustrated in Scheme 36, Example 5. In this procedure, the monoacid **S36.26** is reacted with ethyl 2-bromo-3-phenylpropionate **S36.27** and diisopropylethylamine in dimethylformamide at 80 °C to afford the mixed diester product **S36.28**.

20 Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **S36.27**, different haloesters **S36.7**, the corresponding products **S36.4** are obtained.

Scheme 36

Scheme 36 Example 1**Scheme 36 Example 2****Scheme 36 Example 3**

Scheme 36 Example 4**Scheme 36 Example 5**

Scheme 37 illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

5 The compounds are prepared directly or indirectly from the phosphonic acids S34.6. In one alternative, the phosphonic acid is coupled with the hydroxyester S37.2, using the conditions described previously in Schemes 34-36, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsunobu reaction, to afford the diester 10 product S37.3 in which the ester substituents are identical.

This method is illustrated in Scheme 37, Example 1. In this procedure, the phosphonic acid S34.6 is reacted with three molar equivalents of butyl lactate

S37.5 in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70 °C, to afford the diester S37.6.

Using the above procedure, but employing, in place of butyl lactate S37.5, different hydroxyesters S37.2, the corresponding products S37.3 are obtained.

Alternatively, the diesters S37.3 are obtained by alkylation of the phosphonic acid S34.6 with a haloester S37.1. The alkylation reaction is performed as described in Scheme 36 for the preparation of the esters S36.4.

This method is illustrated in Scheme 37, Example 2. In this procedure, 10 the phosphonic acid S34.6 is reacted with excess ethyl 3-bromo-2-methylpropionate S37.7 and diisopropylethylamine in dimethylformamide at ca. 80 °C, as described in *Anal. Chem.*, 1987, 59, 1056, to produce the diester S37.8.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate S37.7, different haloesters S37.1, the corresponding products 15 S37.3 are obtained.

The diesters S37.3 are also obtained by displacement reactions of activated derivatives S34.7 of the phosphonic acid with the hydroxyesters S37.2. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme 36. The displacement reaction is 20 performed in the presence of an excess of the hydroxyester, to afford the diester product S37.3 in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters S37.3 in which the ester substituents are different.

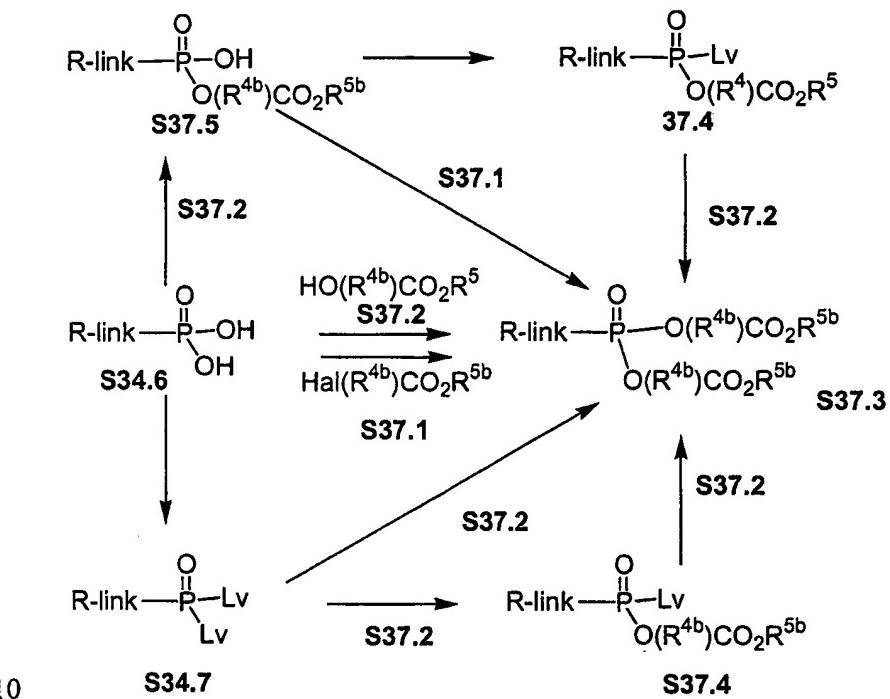
The methods are illustrated in Scheme 37, Examples 3 and 4. As shown 25 in Example 3, the phosphoryl dichloride S35.22 is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate S37.9 in tetrahydrofuran containing potassium carbonate, to obtain the diester product S37.10.

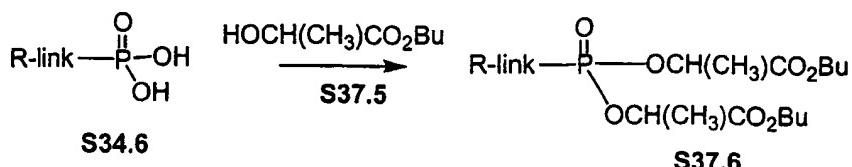
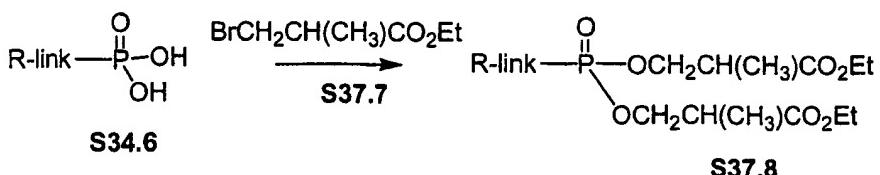
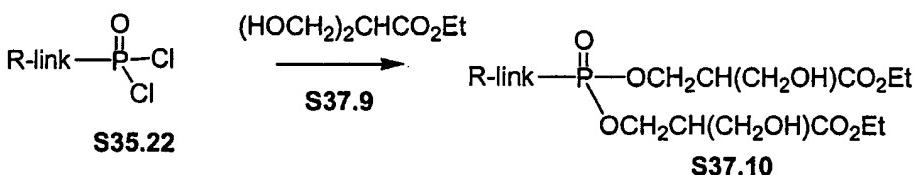
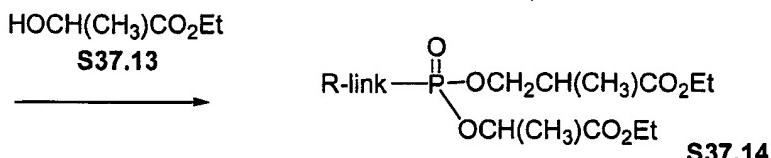
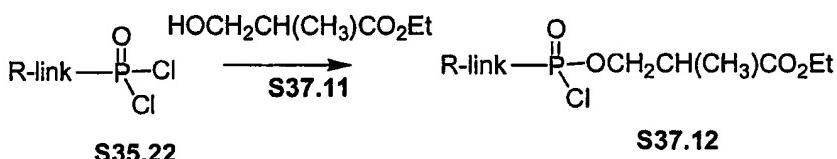
Using the above procedure, but employing, in place of ethyl 3-hydroxy- 30 2-(hydroxymethyl)propionate S37.9, different hydroxyesters S37.2, the corresponding products S37.3 are obtained.

Scheme 37, Example 4 depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride S35.22 and ethyl 2-methyl-3-hydroxypropionate S37.11, to yield the monoester product S37.12. The reaction is conducted in acetonitrile at 70° in the presence of diisopropylethylamine. The 5 product S37.12 is then reacted, under the same conditions, with one molar equivalent of ethyl lactate S37.13, to give the diester product S37.14.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate S37.11 and ethyl lactate S37.13, sequential reactions with different hydroxyesters S37.2, the corresponding products S37.3 are obtained.

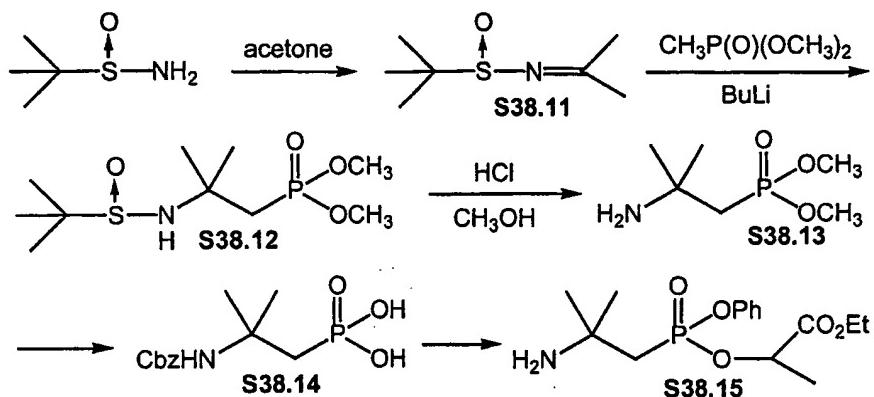
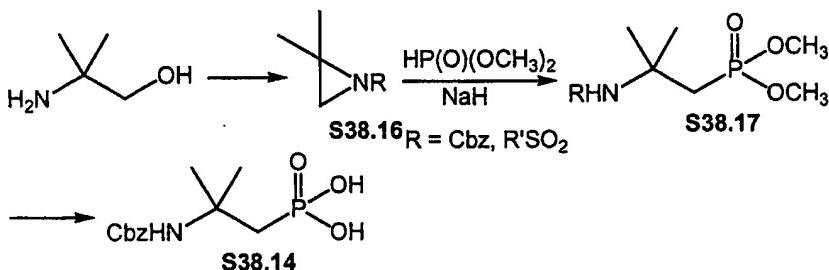
Scheme 37



Scheme 37 Example 1**Scheme 37 Example 2****Scheme 37 Example 3****Scheme 37 Example 4**

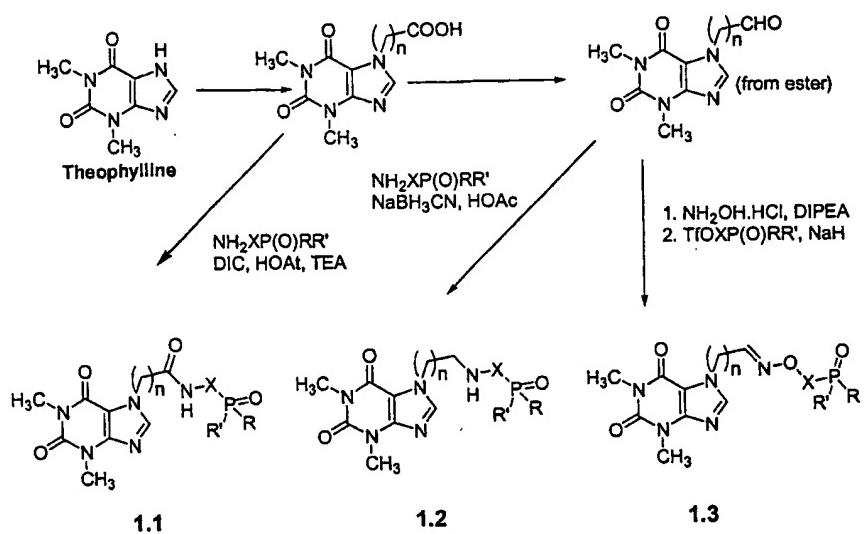
- 5 2,2-Dimethyl-2-aminoethylphosphonic acid intermediates can be
prepared by the route in Scheme 5. Condensation of 2-methyl-2-
propanesulfinamide with acetone give sulfinyl imine **S38.11** (*J. Org. Chem.*
1999, 64, 12). Addition of dimethyl methylphosphonate lithium to **S38.11**
afford **S38.12**. Acidic methanolysis of **S38.12** provide amine **S38.13**. Protection
10 of amine with Cbz group and removal of methyl groups yield phosphonic acid

S38.14, which can be converted to desired S38.15 (Scheme 38a) using methods reported earlier on. An alternative synthesis of compound S38.14 is also shown in Scheme 38b. Commercially available 2-amino-2-methyl-1-propanol is converted to aziridines S38.16 according to literature methods (*J. Org. Chem.* 1992, 57, 5813; *Syn. Lett.* 1997, 8, 893). Aziridine opening with phosphite give S38.17 (*Tetrahedron Lett.* 1980, 21, 1623). Reprotection of S38.17 affords S38.14.

Scheme 38a**Scheme 38b**

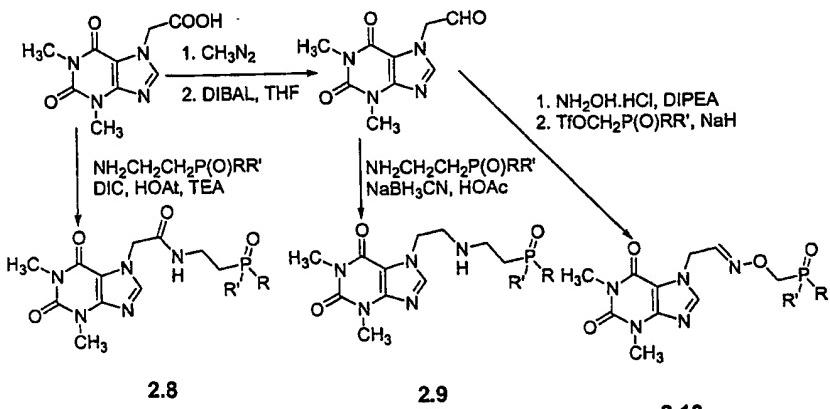
The invention will now be illustrated by the following non-limiting Examples.

Example 1. Synthesis of Representative Compounds the Invention



Theophylline is readily converted to N-7 carboxylic esters by simply alkylation. The ester is first saponified to the corresponding acid derivative. The acid derivative is reacted with aminophosphonate, DIC, and HOAt to afford compounds of formula 1.1. The ester is reduced to aldehyde derivative, for example by reductive amination with an aminophosphonate, NaBH_3CN , and HOAc to provide compounds of formula 1.2. The aldehyde can also be reacted with hydroxylamine hydrochloride, followed by a triflated phosphonate to give compounds of formula 1.3.

Example 2. Synthesis of Representative Compounds of the Invention

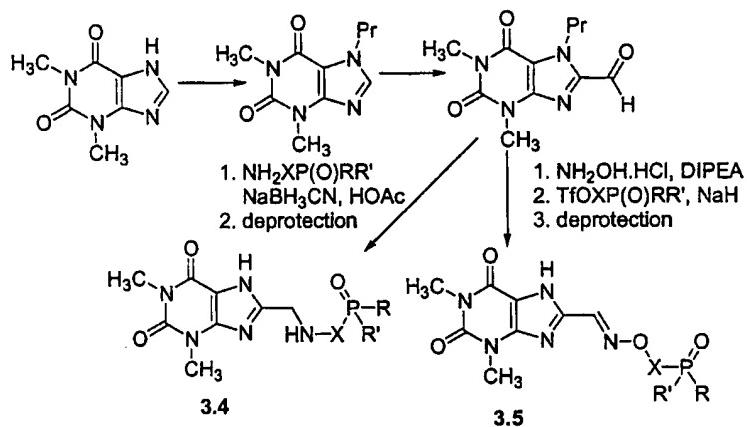


Compounds 2.8, 2.9, and 2.10, can be prepared as follows.

Theophylline-7-acetic acid (J. Amer. Che. Soc. 1967, 89, 308) is reacted with aminoethyl phosphonate, DIC, HOAt to afford compound 2.8. Alternatively, the acid is converted to methyl ester by reaction with diazomethane, followed by the reduction with DIBAL in THF to give N-7-aldehyde derivate. This aldehyde is reacted with hydroxylamine hydrochloride in the presence of TEA, followed by treating with NaH and triflated phosphonate to furnish the desired product 2.10. The reductive amination of the aldehyde with aminoethyl phosphonate, NaBH₃CN, and HOAc gives compound 2.9.

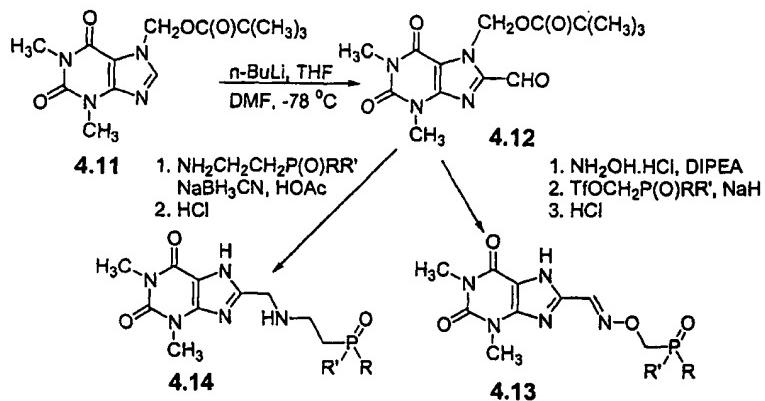
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Example 3. Synthesis of Representative Compounds of the Invention

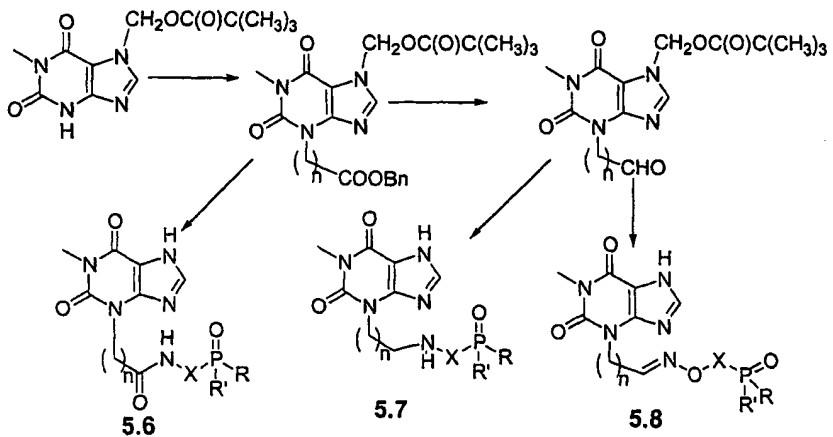


15

Theophylline (J. Gen. Chem. USSR 1946, 16, 179; Chem. Ber. 1962, 95 403) is protected with adequate protecting group, followed by reaction with n-BuLi, DMF to generat the 6-formaldehyde derivative. This aldehyde is converted to analog 3.4 by the reductive amination with aminophosphonate followed by the removal of N-7 protecting group. Analog 3.5 is prepared from 20 the aldehyde in 3 steps. First the aldehyde is reacted with hydroxylamine to give the corresponding oxime, followed by reaction with a triflated phosphonate and deprotection of N-7 protecting group to provide a compound of formula 3.5.

Example 4. Synthesis of Representative Compounds of the Invention

5 Theophylline is protected with acid labile group by treating with NaH and (pivaloyloxy)mehtyl chloride to give 4.11 (J. O. C. 1980, 45, 1711). Compound 4.11 is treated with $n\text{-BuLi}$ at -78°C in THF and reacted with DMF to give 4.12. The reductive amination of 4.12 with aminoethyl phosphonate, NaBH_3CN , and HOAc , followed by aqueous hydrochloric acid furnishes the product 4.14. Aldehyde 4.12 can also be reacted with hydroxylamine hydrochloride in the presence base, followed by reaction with NaH and a triflated phosphonate, and deprotection with aqueous HCl to give compound 4.13.

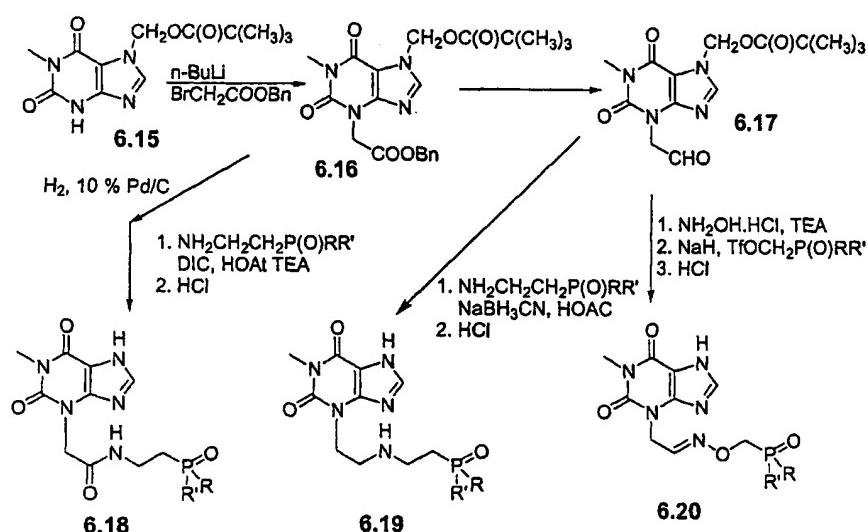
15 Example 5. Synthesis of Representative Compounds of the Invention

The synthesis of analogs 5.6, 5.7, and 5.8 is illustrated above.

1-Methylxanthine is selectively protected with pivaloyloxymethyl group followed by alkylation at N-4, to provide a key intermediate for preparing 5.6-5.8.

Hydrogenation to convert the benzyl ester to the acid followed by reaction with 5 aminophosphonate gives compound 5.6. Reduction of the benzyl ester to the alcohol, followed by reductive amination with aminophosphonate and acid deprotection affords compound 5.7. Analog 5.8 is prepared from the aldehyde stepwise with hydroxylamine, triflated phosphonate, and deprotection of N-7.

10 Example 6. Synthesis of Representative Compounds of the Invention



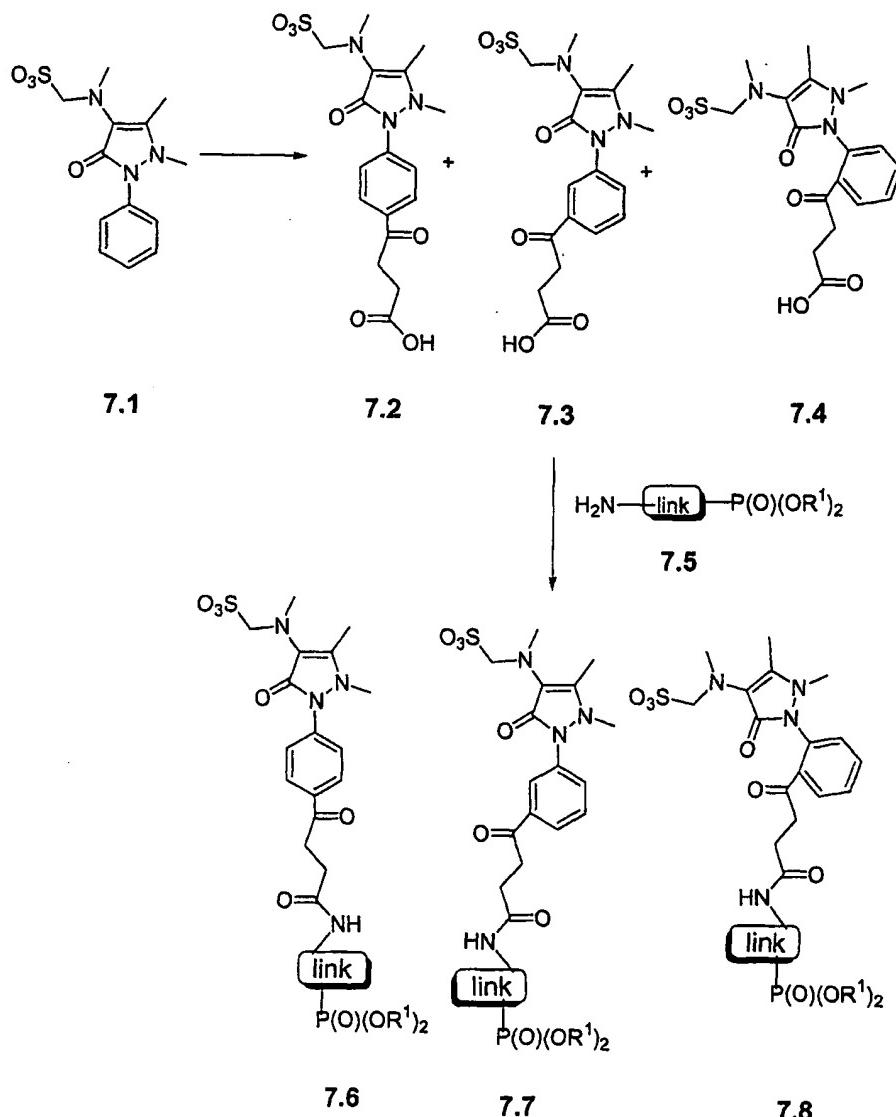
Compounds of formulae 6.18, 6.19, and 6.20 can be synthesized as outlined above. Compound 6.15 is prepared as previously reported (J. O. C.

15 1980, 45, 1711). N-7 protected 1-N-methylxanthine 6.15 is alkylated with benzyl bromoacetate to provide intermediate 6.16. The hydrogenation of 6.16 in the presence of 10 % Pd/C gives the corresponding acid derivative. The acid derivative is reacted with aminoethyl phosphonate, DIC, and HOAt, and deprotected with aqueous HCl to furnish 6.18. Benzyl ester 6.16 can be reduced 20 with DIBAL in THF to the corresponding aldehyde 6.17. Aldehyde 6.17 is reacted with hydroxylamine hydrochloride in the presence of base (e.g. TEA), followed by reaction with NaH and triflated phosphonate, and deprotection with aqueous HCl to give compound 6.20. The reductive amination of 6.17 with

aminoethyl phosphonate, NaBH₃CN, and HOAc, followed by deprotection with aqueous HCl furnishes the desired product 6.19.

Example 7. Synthesis of Representative Compounds of the Invention

5



Metamizole 7.1 can be purchased from Sigma (Cat. No. D8890) or

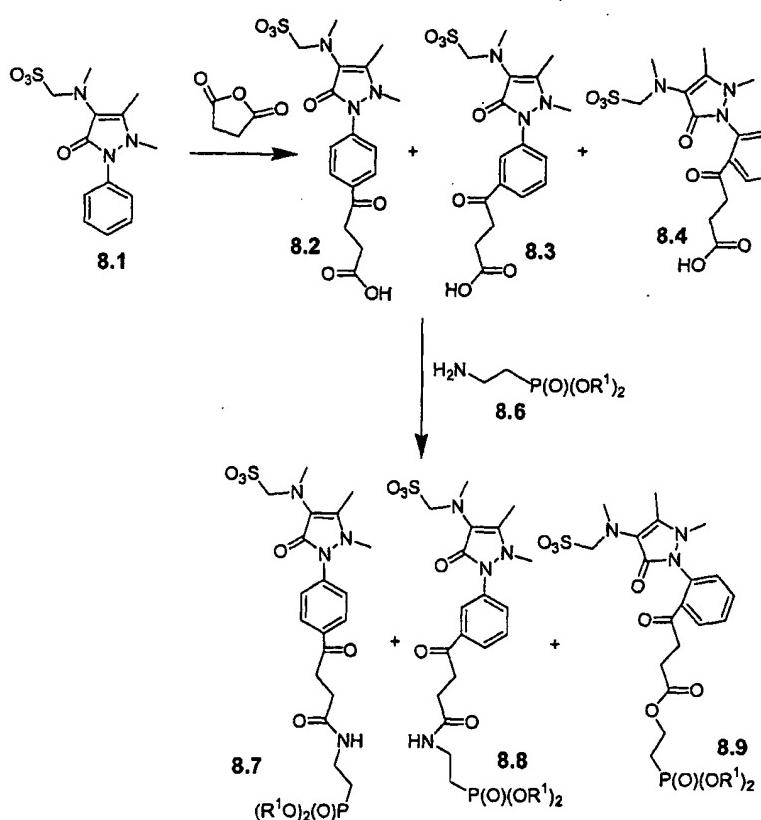
prepared as in DE 259577 and DE 254711. The preparation of the phosphonate

linkage to 7.1 through the carboxylic acid derivatives 7.2, 7.3 and 7.4 to give

10 compounds of formula 7.6, 7.7, and 7.8 is illustrated above. Compound 7.1 is dissolved in a suitable solvent such as, for example, DCM and is then treated

with AlCl_3 and a suitable anhydride, for example, succinic anhydride as described in *Tett. Lett.* 42 (2001) 1467-1469. The acylated products are purified using reverse phase HPLC or flash chromatography on silica gel to give carboxylic acid derivatives **7.2**, **7.3** and **7.4**. Metamizole derivatives **7.2**, **7.3** and **7.4** are independently dissolved in a suitable solvent such as, for example, DMF and treated with an amine phosphonic acid ester of the general formula **7.5** in the presence of a suitable coupling reagent and tertiary organic base to afford the amides **7.6**, **7.7**, and **7.8**.

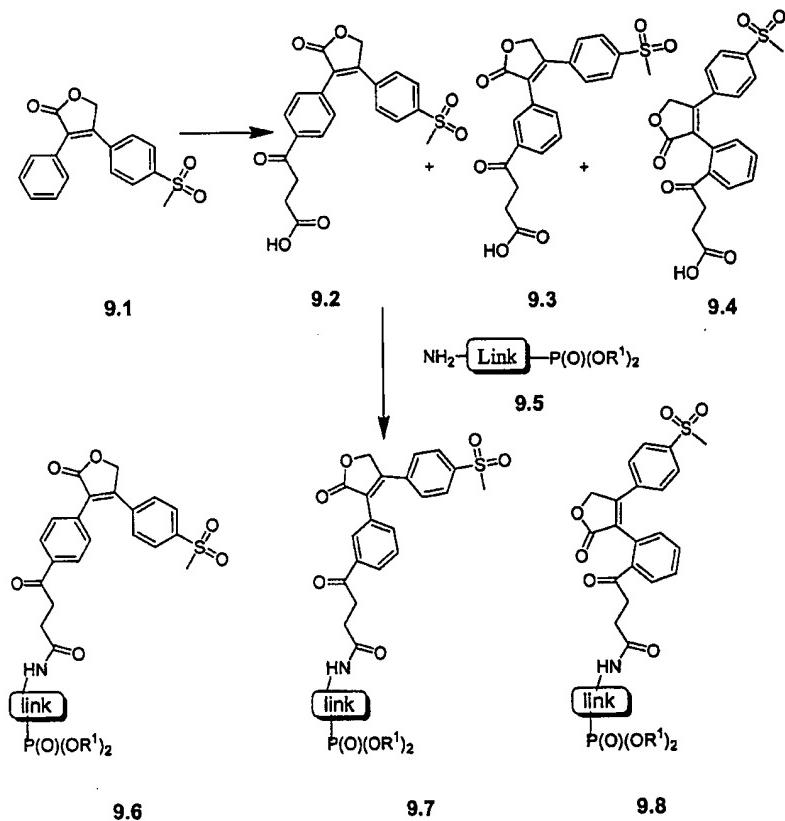
10 Example 8. Synthesis of Representative Compounds of the Invention



For example, **8.2**, **8.3**, or **8.4** is dissolved in DMF and treated with 3 equivalents of (benzotriazol-1-yloxy)tritylolidinophosphonium hexafluorophosphate (PYBOP, Sigma) and 6 equivalents of diisopropylamine. The activated esters of **8.2**, **8.3** and **8.4** are then independently treated with 3

equivalents of the hydrochloride salt of diethyl 2-aminoethyl-1-phosphonate **8.6** which is prepared as described in J.Med.Chem 41 4439-4452. The final products are purified by reverse phase or flash chromatography on silica gel to give amides **8.7**, **8.8** and **8.9**. Using the above procedure but employing different 5 phosphonate reagents in the place of **8.6** additional compounds of the invention can be prepared.

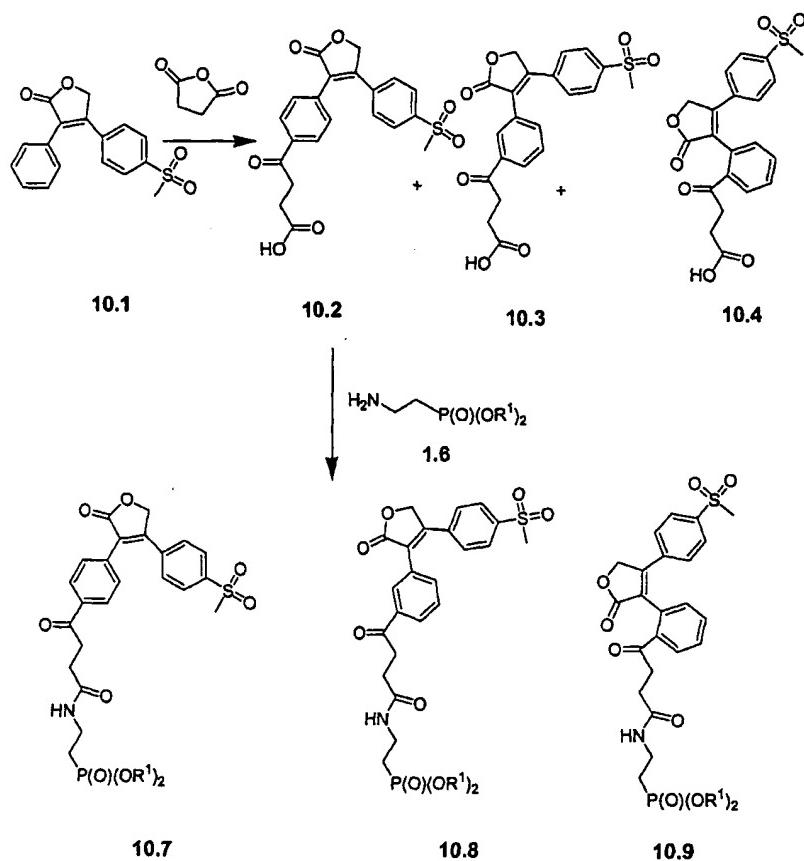
Example 9. Synthesis of Representative Compounds of the Invention



10 Rofecoxib derivative **9.1** can be obtained as described in US5474995 Example 24. Compound **1.1** is dissolved in a suitable solvent such as, for example, DCM and is then treated with AlCl₃ and a suitable anhydride, for example, succinic anhydride as described in Tett. Lett 42 (2001) 1467-1469. The 15 acylated products are purified using reverse phase HPLC or flash chromatography on silica gel to give carboxylic acid derivatives **9.2**, **9.3** and **9.4**. Rofecoxib derivatives **9.2**, **9.3** and **9.4** are independently dissolved in a suitable

solvent such as, for example, DMF and is then treated with an amine phosphonic acid ester of the general formula 9.5 in the presence of a suitable coupling reagent and tertiary organic base to afford the amides 9.6, 9.7 and 9.8.

5 Example 10. Synthesis of Representative Compounds of the Invention

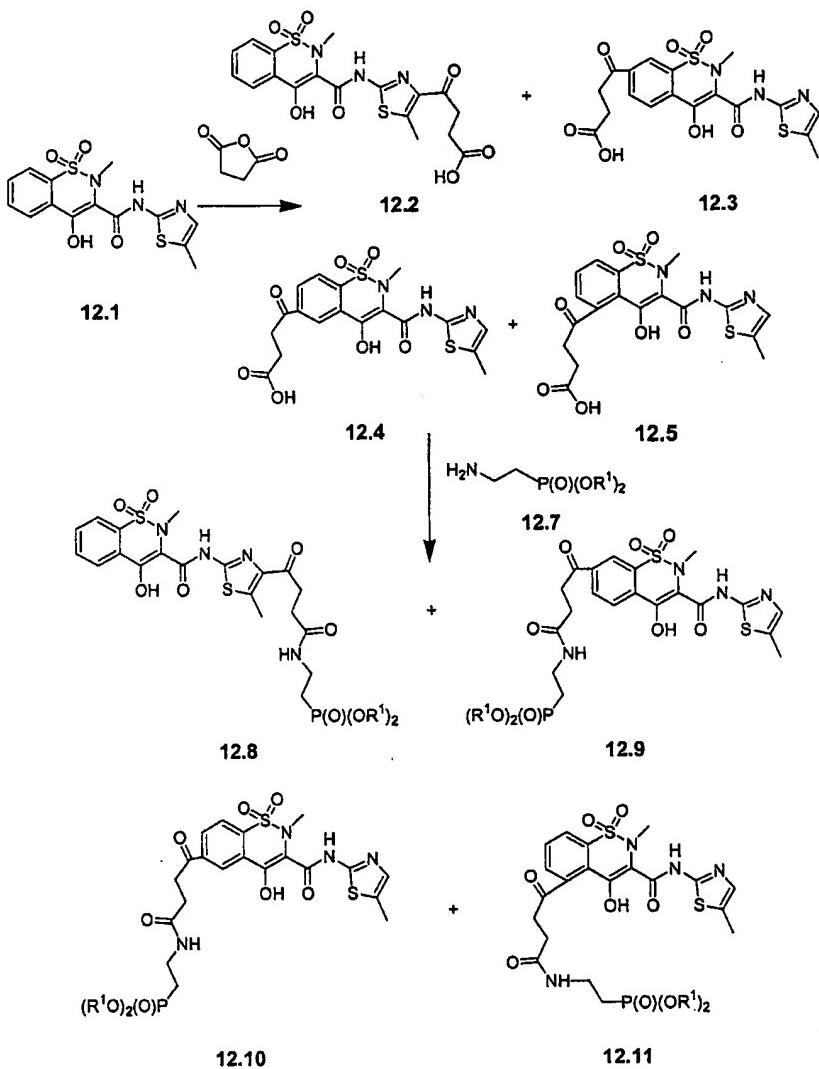


- Compound 10.2, 10.3, or 10.4 dissolved in DMF, is treated with 3
 10 equivalents of (benzotriazol-1-yloxy)tripyrrolidinophosphonium
 hexafluorophosphate (PYBOP, Sigma) and 6 equivalents of diisopropylamine.
 The activated esters of 10.2, 10.3 and 10.4 are then independently treated with 3
 equivalents of the hydrochloride salt of diethyl 2-aminoethyl-1-phosphonate 10.6
 which is prepared as described in J.Med.Chem 41 4439-4452. The final products
 15 are purified by reverse phase or flash chromatography on silica gel to give
 amides 10.7, 10.8 and 10.9. Using the above procedure but employing different

acid ester of the general formula 11.6 in the presence of a suitable coupling reagent and tertiary organic base to afford the amides 11.7, 11.8, 11.9, and 11.10.

Example 12. Synthesis of Representative Compounds of the Invention

5

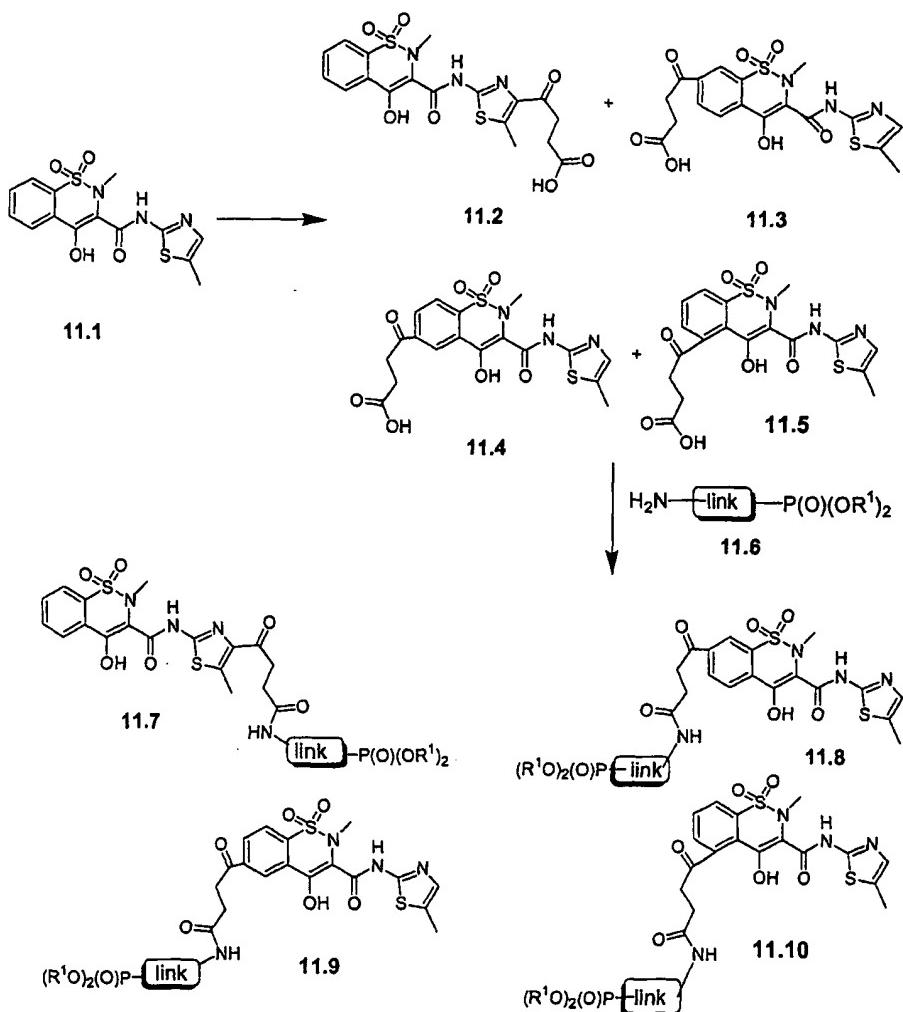


Compound 12.2 12.3, 12.4, or 12.5 is dissolved in DMF and treated with 3 equivalents of (benzotriazol-1-yl)oxo)tritylolidinophosphonium hexafluorophosphate (PYBOP, Sigma) and 6 equivalents of diisopropylamine. The activated esters of compounds 12.2, 12.3, 12.4 and 12.5 are then independently treated with 3 equivalents of the hydrochloride salt of diethyl 2-

phosphonate reagents in the place of compound 8.6 additional compounds of the invention can be prepared.

Example 11. Synthesis of Representative Compounds of the Invention

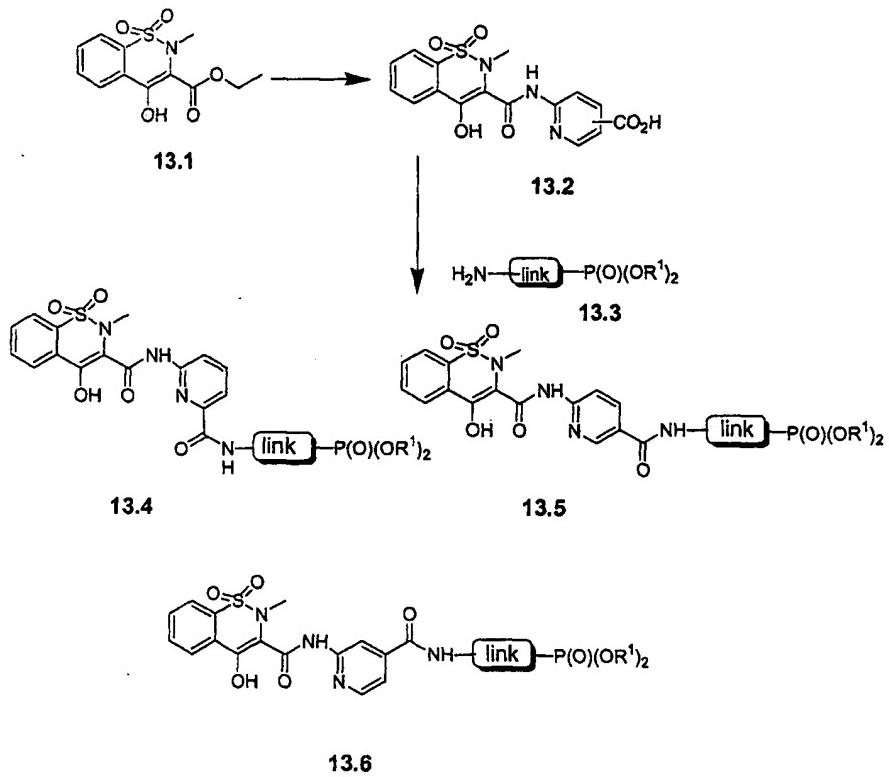
5



Compound 11.1 is dissolved in a suitable solvent such as, for example, DCM and is then treated with AlCl_3 and a suitable anhydride, for example, succinic anhydride as described in Tett. Lett 42 (2001) 1467-1469. The acylated products are purified using reverse phase HPLC or flash chromatography on silica gel to give carboxylic acid derivatives 11.2, 11.3, 11.4 and 11.5. Compounds 11.2, 11.3, 11.4 and 11.5 are independently dissolved in a suitable solvent such as, for example, DMF and is then treated with an amine phosphonic

aminoethyl-1-phosphonate 12.7 which is prepared as described in J.Med.Chem 41 4439-4452. The final products are purified by reverse phase or flash chromatography on silica gel to give amides 12.8, 12.9, 12.10 and 12.11. Using the above procedure but employing different phosphonate reagents in the place of 12.7 additional compounds of the invention can be prepared.

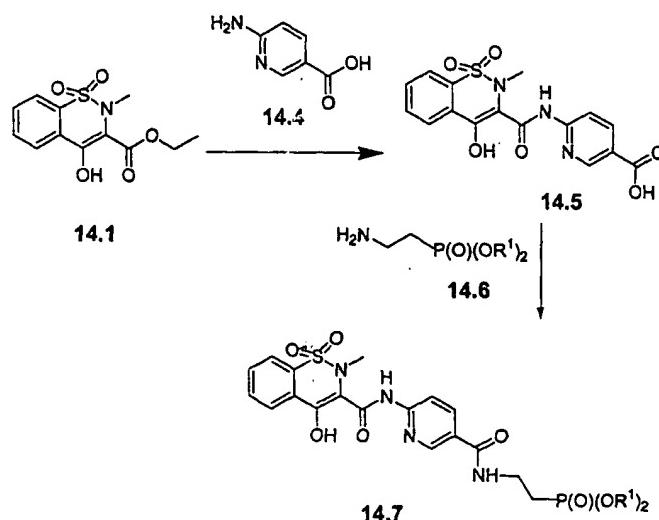
5 Example 13. Synthesis of Representative Compounds of the Invention



Intermediate 13.1 is available from Sigma or alternatively can be
10 prepared as described in US 3,591,584. Intermediate 13.2 can be prepared as described in US 3,891,637 example XI or as described in *J. Med. Chem.* 14 1171-1175 (1971) and coupled to the appropriately substituted aminonicotinic acid using the procedure described in *J. Med. Chem.* 30 678-682 1987.

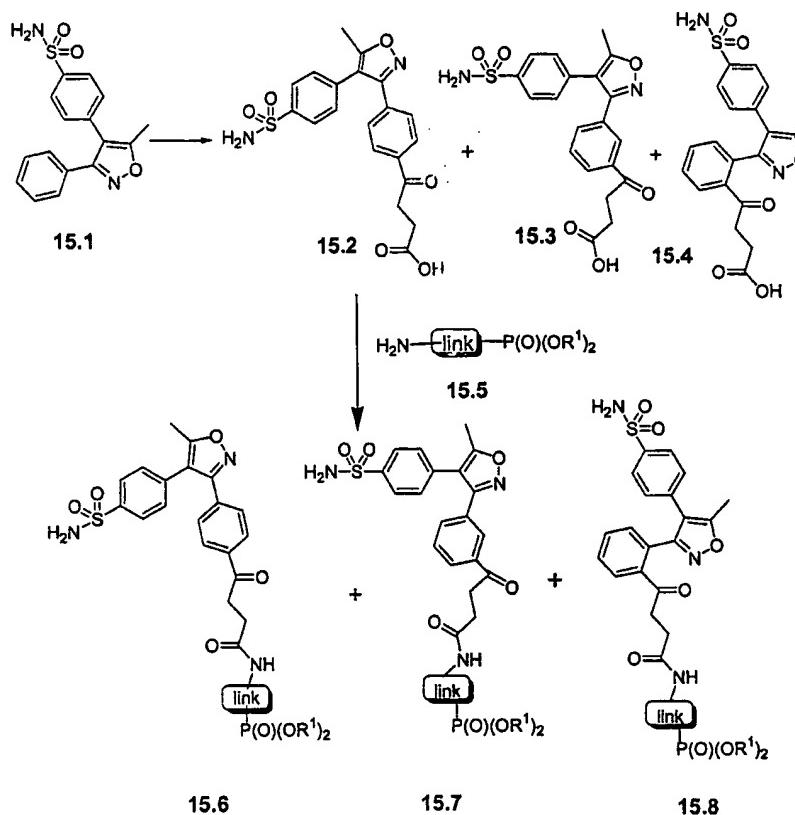
15 Piroxicam derivative 13.2 is treated with an amine phosphonic acid ester of the general formula 13.3 in the presence of a suitable coupling reagent and tertiary organic base to afford the amides 13.4, 13.5, and 13.6.

Example 14. Synthesis of Representative Compounds of the Invention



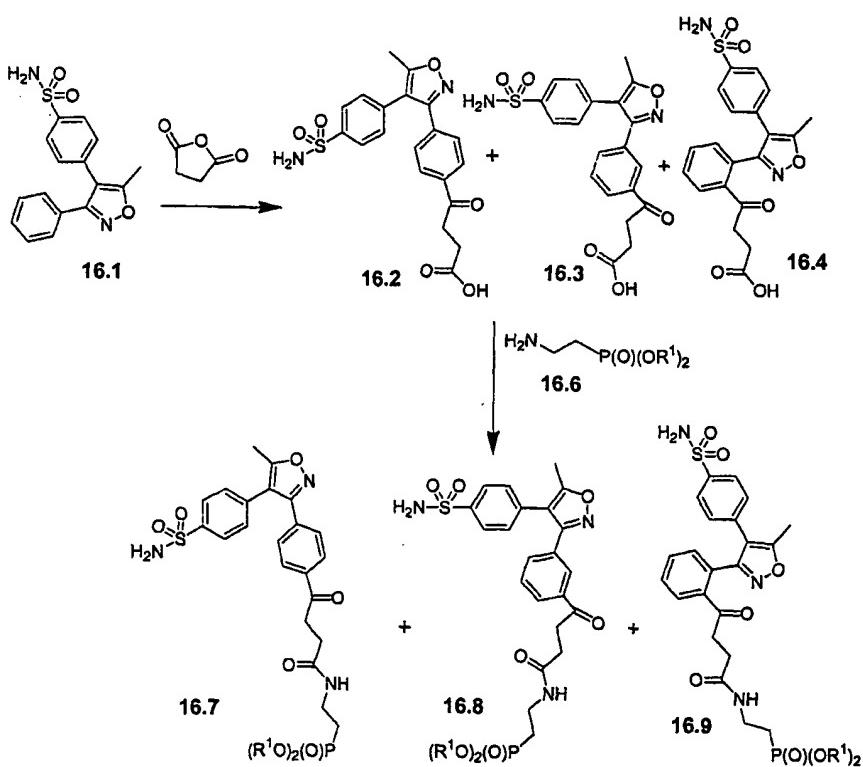
Compound 14.1 and 6-aminonictonic acid are dissolved in a suitable solvent such as xylene and refluxed with active carbon to give intermediate 14.5. Piroxicam derivative 14.5 is then dissolved in anhydrous DMF and treated with 3 equivalents of *O*-(7-azabenzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (Sigma) and 6 equivalents of diisopropylethylamine. The activated ester of 14.5 is then treated with 3 equivalents of the hydrochloride salt of diethyl 2-aminoethyl-1-phosphonate 14.6 which is prepared as described in J.Med.Chem 41 4439-4452, to form the amide 14.7 which is purified by reverse phase or normal phase chromatography. Using the above procedure but employing different phosphonate reagents in the place of compound 14.6 additional compounds of the invention can be prepared.

Example 15. Synthesis of Representative Compounds of the Invention



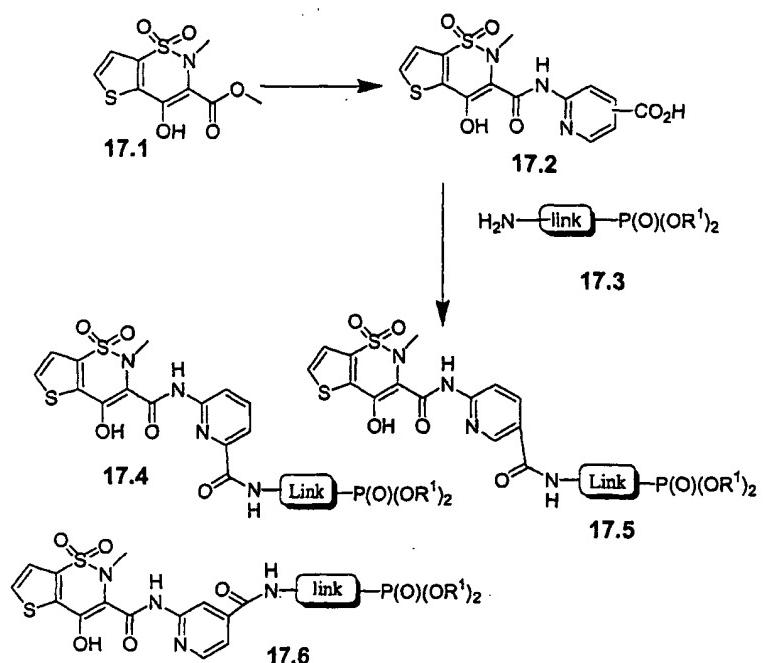
5 Valdecoxib derivative 15.1 can be obtained as described in US5633272
 Example 1. Compound 15.1 is dissolved in a suitable solvent such as, for
 example, DCM and is treated with AlCl₃ and a suitable anhydride, for example,
 succinic anhydride as described in Tett. Lett 42 (2001) 1467-1469. The acylated
 products are purified using reverse phase HPLC or flash chromatography on
 10 silica gel to give carboxylic acid derivatives 15.2, 15.3 and 15.4. Valdecoxib
 derivatives 15.2, 15.3 and 15.4 are independently dissolved in a suitable solvent
 such as, for example, DMF and treated with an amine phosphonic acid ester of
 the general formula 15.5 in the presence of a suitable coupling reagent and
 tertiary organic base to afford the amides 15.6, 15.7, and 15.8.

Example 16. Synthesis of Representative Compounds of the Invention

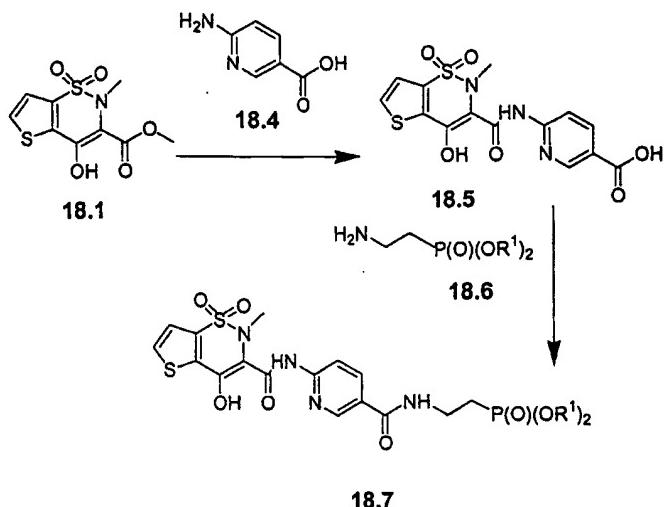


Compound 16.2, 16.3, or 16.4 dissolved in DMF, is treated with 3 equivalents of (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma) and 6 equivalents of diisopropylamine. The activated esters of 16.2, 16.3 and 16.4 are then independently treated with 3 equivalents of the hydrochloride salt of diethyl 2-aminoethyl-1-phosphonate 16.6 which is prepared as described in J.Med.Chem 41 4439-4452. The final products are purified by reverse phase or flash chromatography on silica gel to give amides 16.7, 16.8 and 16.9. Using the above procedure but employing different phosphonate reagents in the place of 16.6 additional compounds of the invention can be prepared.

Example 17. Synthesis of Representative Compounds of the Invention

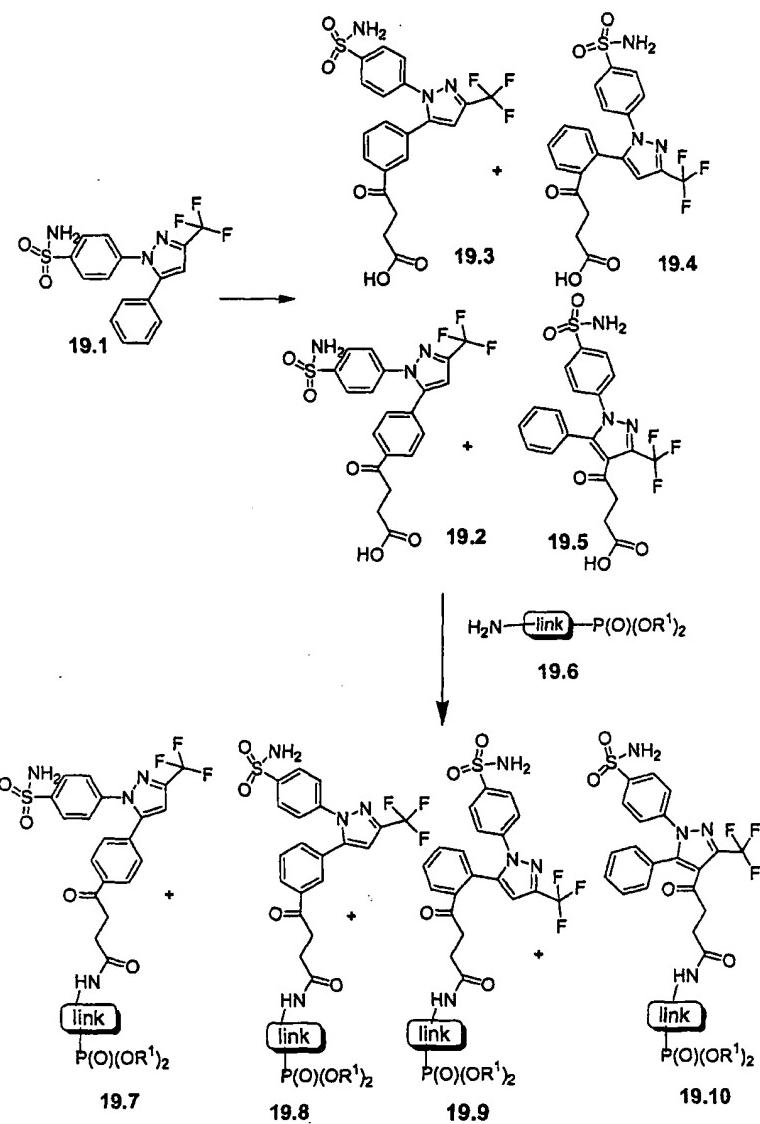


5 Intermediate 17.1 is prepared as described in US 4,076,709 example 9 or
as described in *J. Med. Chem.* 30 678-682 1987. Intermediate 17.1 is converted
to intermediate 17.2 using the appropriately substituted aminonicotinic acid.
10 Intermediate 17.2 is treated with an amine phosphonic acid ester of the general
formula 17.3 in the presence of a suitable coupling reagent and tertiary organic
base to afford the amides 17.4, 17.5 and 17.6.

Example 18. Synthesis of Representative Compounds of the Invention

Compound 18.1 and 6-aminonictonic acid are dissolved in a suitable solvent such as xylene and refluxed with active carbon to give intermediate 18.5. 5 which is purified by reverse phase or normal phase chromatography. Tenoxicam derivative 18.5 is then dissolved in anhydrous DMF and treated with 3 equivalents of *O*-(7-azabenzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (Sigma) and 6 equivalents of diisopropylethylamine. The activated ester of 18.5 is then treated with 3 equivalents of the hydrochloride salt 10 of diethyl 2-aminoethyl-1-phosphonate 18.6 which is prepared as described in *J.Med.Chem* 41 4439-4452 to give compound 18.7 which is purified by reverse phase or normal phase chromatography. Using the above procedure but employing different phosphonate reagents in the place of compound 18.6 additional compounds of the invention can be prepared.

Example 19. Synthesis of Representative Compounds of the Invention



5 Celecoxib derivative 19.1 can be obtained as described in US5466823

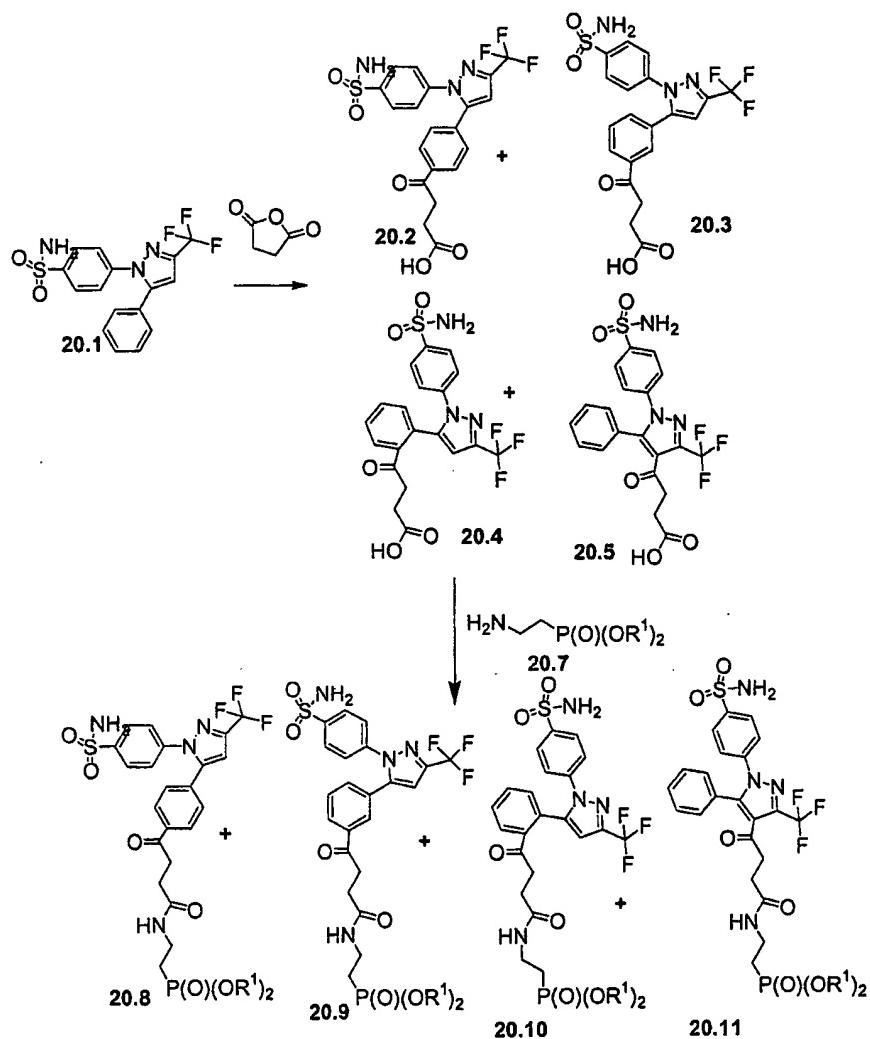
Example (1g). Compound 19.1 is dissolved in a suitable solvent such as, for example, DCM and is then treated with AlCl_3 and a suitable anhydride, for example, succinic anhydride as described in *Tett. Lett.* 42 (2001) 1467-1469. The acylated products are purified using reverse phase HPLC or flash

10 chromatography on silica gel to give carboxylic acid derivatives 19.2, 19.3, 19.4 and 19.5. Celecoxib derivatives 19.2, 19.3, 19.4 and 19.5 are independently

dissolved in a suitable solvent such as, for example, DMF and treated with an amine phosphonic acid ester of the general formula **19.6** in the presence of a suitable coupling reagent and tertiary organic base to afford the amides **19.7**, **19.8**, **19.9** and **19.10**.

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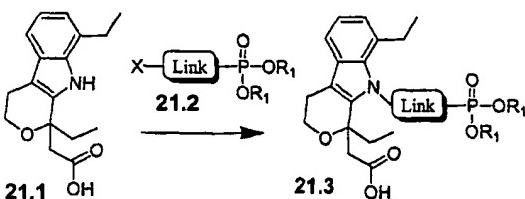
Example 20. Synthesis of Representative Compounds of the Invention



Compound **20.2**, **20.3**, **20.4**, or **20.5** dissolved in DMF, is treated with 3
10 equivalents of (benzotriazol-1-yloxy)tripyrrolidinophosphonium
hexafluorophosphate (PYBOP, Sigma) and 6 equivalents of diisopropylamine.
The activated esters of **20.2**, **20.3** **20.4** and **20.5** are then independently treated

with 3 equivalents of the hydrochloride salt of diethyl 2-aminoethyl-1-phosphonate **20.7** which is prepared as described in *J.Med.Chem* 41 4439-4452. The final products are purified by reverse phase or flash chromatography on silica gel to give amides **20.8**, **20.9**, **20.10** and **20.11**. Using the above procedure
 5 but employing different phosphonate reagents in the place of **20.7** additional compounds of the invention can be prepared.

Example 21. Synthesis of Representative Compounds of the Invention

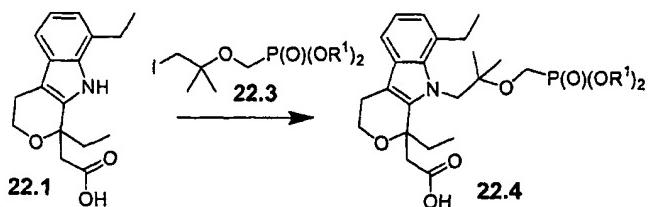


X = Cl, Br, I

10 R¹ = H, alkyl, aryl, haloalkyl, alkenyl, aralkyl, aryl

Etodolac **21.1** can be purchased from Sigma (Cat. No. E0156) or obtained as described in US 3,939,178 Example 477. The indole **21.1** is deprotonated with a suitably strong base such as, for example, KOH or K₂CO₃ in
 15 DMSO or DMF as described in *J. Org. Chem* 64 6102-6105, followed by alkylation with a halide phosphonic acid ester of the general formula **21.2**. The alkylated product is purified by reverse phase or flash chromatography on silica gel to give compound **21.3**.

20 **Example 22. Synthesis of Representative Compounds of the Invention**

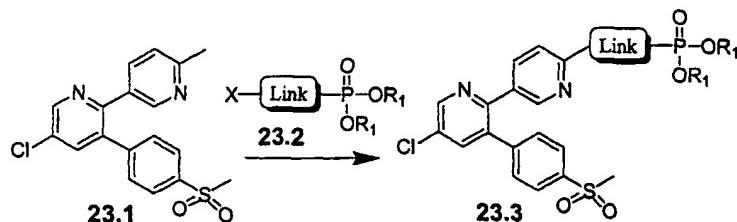


Compound **22.1** is dissolved in DMSO and treated with 6 equivalents of potassium hydroxide, followed by addition of 1.1 equivalents of **22.3** which is

prepared as described in *J.Org.Chem.*, 52 4427. The residue is purified using reverse-phase or normal phase chromatography to give 22.4 Using the above procedure but employing different phosphonate reagents in the place of compound 22.3 additional compounds of the invention can be prepared.

5

Example 23. Synthesis of Representative Compounds of the Invention



$X = I, Br, Cl$

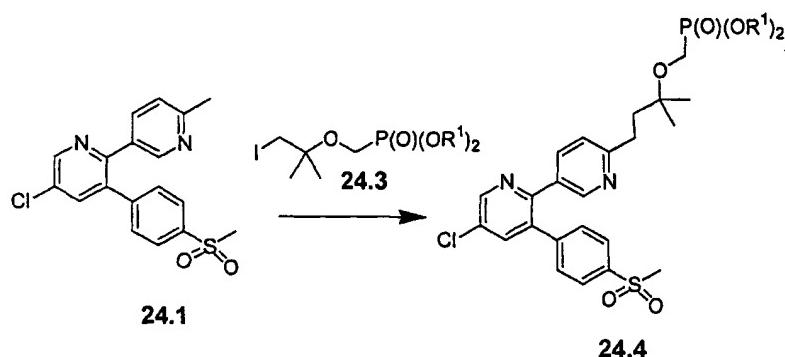
$R^1 = H, \text{alkyl, aryl, haloalkyl, alkenyl, aralkyl, aryl}$

Etoricoxib derivative 23.1 can be obtained as described in US5861419

Example 59. Alternative syntheses for 23.1 are described in *J. Org. Chem.* 2000,

10 65, 8415-8420. The 2-methyl group of the 5-pyridyl ring is deprotonated with a
suitably strong base such as, for example, *n*-BuLi using the procedure described
in *J. Org. Chem.* 1987, 52, 4227 followed by alkylation of the newly formed
carbanion with a halide phosphonic acid ester of the general formula 23.2. The
alkylated product is purified by reverse phase or flash chromatography on silica
15 gel to give compound 23.3.

Example 24. Synthesis of Representative Compounds of the Invention

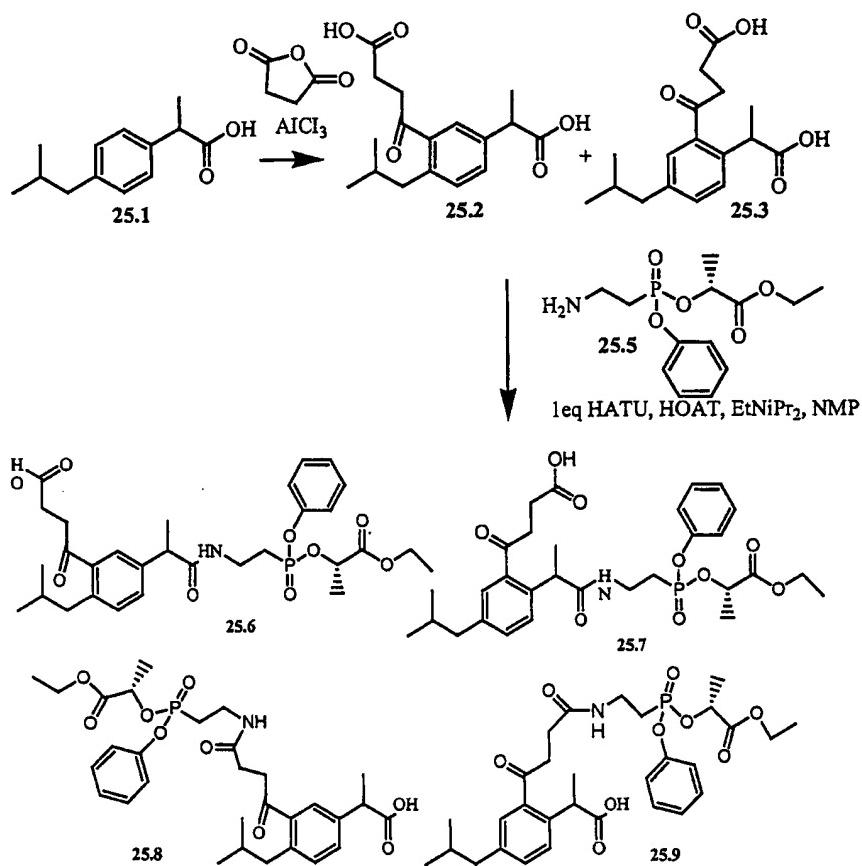


20

1.5 Equivalents of a 1.6 N solution of *n*-butyllithium in hexane is added to a solution of compound 24.1 in anhydrous ethyl ether at 0°C. The solution is treated with 4 equivalents of compound 24.3 which is prepared as described in *J.Org.Chem.*, 52 4427. The residue is purified using reverse-phase or normal phase chromatography to give 24.4. Using the above procedure but employing different phosphonate reagents in the place of compound 24.3 additional compounds of the invention can be prepared.

Example 25. Synthesis of Representative Compounds of the Invention

10

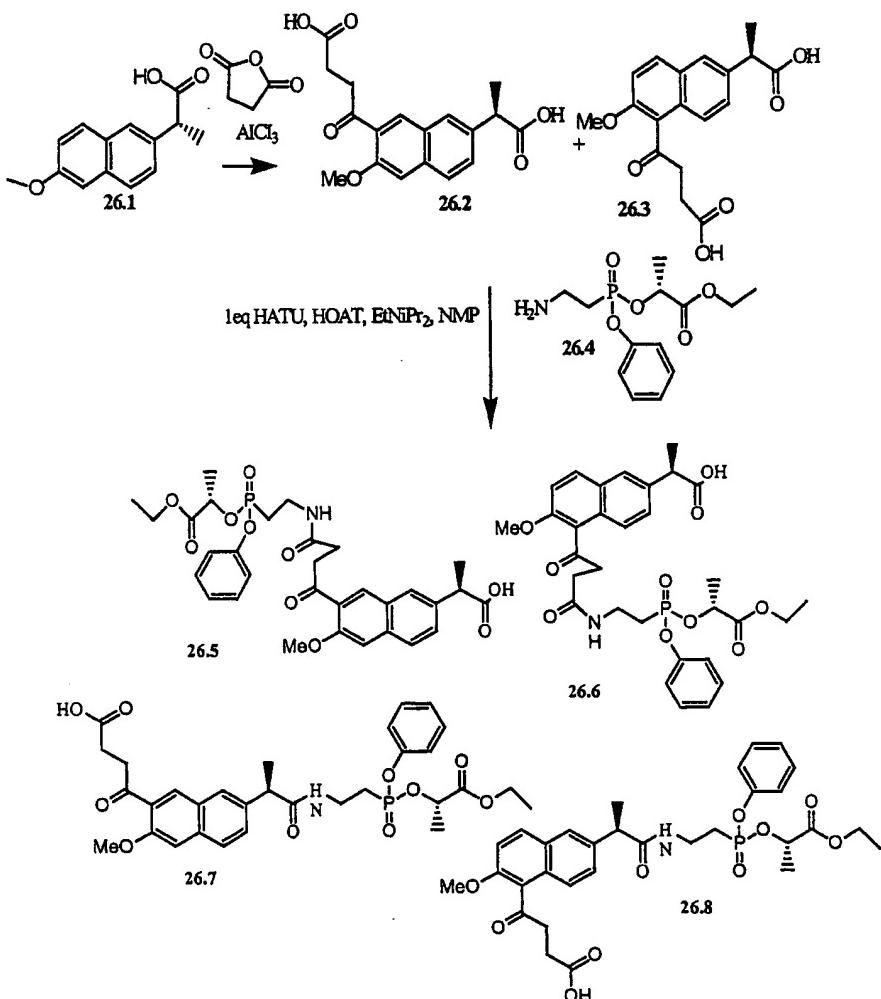


Ibuprofen (US3,385,886), commercially available from Sigm-Aldrich, is converted to dicarboxylic acids 25.2 and 25.3 by the action of succinic anhydride in the presence of aluminum trichloride in a suitable solvent (carbon disulfide, nitrobenzene, dichloroethane). Conversion 25.2 and 25.3 to phosphonate

prodrugs occurs by the addition of 1.5 equivalents HOAT, HATU, diisopropylethylamine to **25.2** and **25.3** followed by the addition of **25.5** all in a suitable solvent such as NMP, DMF, THF, or dichloroethane. Separation of the final mixture leads to the desired materials **25.6** and **25.7**, **25.8** and **25.9**.

5

Example 26. Synthesis of Representative Compounds of the Invention



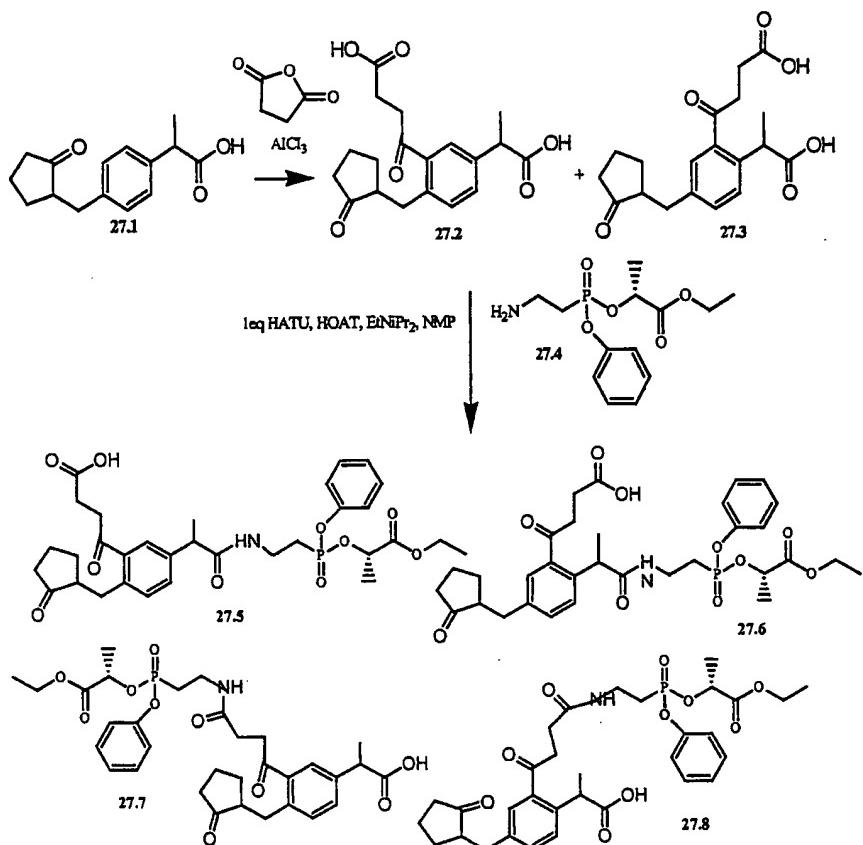
10

Naproxen (US3,904,683), commercially available from Sigma-Aldrich, is converted to dicarboxylic acids **26.2** and **26.3** by the action of succinic anhydride in the presence of aluminum trichloride in a suitable solvent such as carbon disulfide, nitrobenzene, and dichloroethane. Conversion of **26.2** and **26.3** to

phosphonate prodrugs occurs by the addition of 1.5 equivalents HOAT, HATU, and diisopropylethylamine to **26.2** and **26.3** followed by the addition of **26.4** all in a suitable solvent such as NMP, DMF, THF, or dichloroethane. Separation of the final mixture leads to the desired materials **26.5**, **26.6**, **26.7**, **26.8**.

5

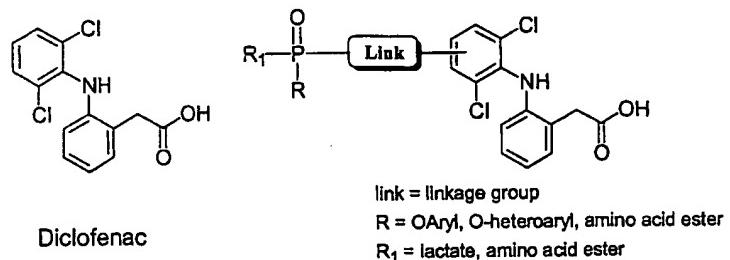
Example 27. Synthesis of Representative Compounds of the Invention



10 Loxoprofen (U.S. Patent No. 4,400,534), commercially available from Sigm-Aldrich, is converted to dicarboxylic acids **27.2** and **27.3** by the action of succinic anhydride in the presence of aluminum trichloride in a suitable solvent such as carbon disulfide, nitrobenzene, and dichloroethane. Conversion **27.2** and **27.3** to phosphonate prodrugs occurs by the addition of 1.5 equivalents HOAT,
15 HATU, and diisopropylethylamine to **27.2** and **27.3** followed by the addition of **27.4** all in a suitable solvent such as NMP, DMF, THF, or dichloroethane.

Separation of the final mixture leads to the desired materials 27.5, 27.6, 27.7 and 27.8.

Example 28. Synthesis of Representative Compounds of the Invention



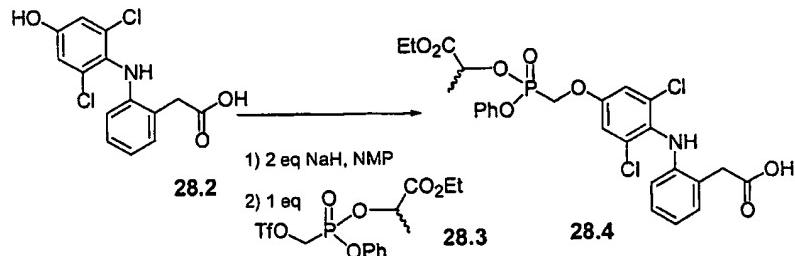
5

28.1

Representative compounds of the invention (28.1) are illustrated above. A linkage group is a portion of the structure that links two substructures, one of which is Diclofenac having the general formula above, the other a phosphonate moiety bearing the appropriate R and R₁ groups. The linkage typically has at least one uninterrupted chain of atoms other than hydrogen. The R and R₁ groups can be both natural and un-natural amino acid esters linked through the amine nitrogen, or alternatively, one of the groups can be substituted for oxygen linked aryl, alkyl, aralkyl group. Alternatively one of the groups may be an oxygen linked aryl, alkyl, aralkyl group and the other lactate ester.

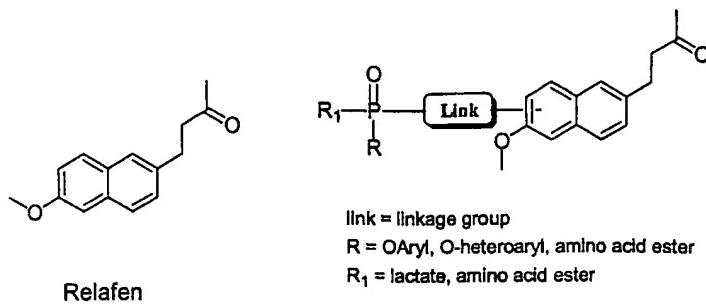
15

The preparation of a representative compound of the invention is illustrated below.



Compound 28.2 (available from Sigma-Aldrich) is reacted with 3 equivalents of a strong base (for example, NaH, KH, NaHMDS, KHMDS, LDA) 20 in a polar aprotic solvent (DMF, DMSO, NMP, DMA, THF) for a period of

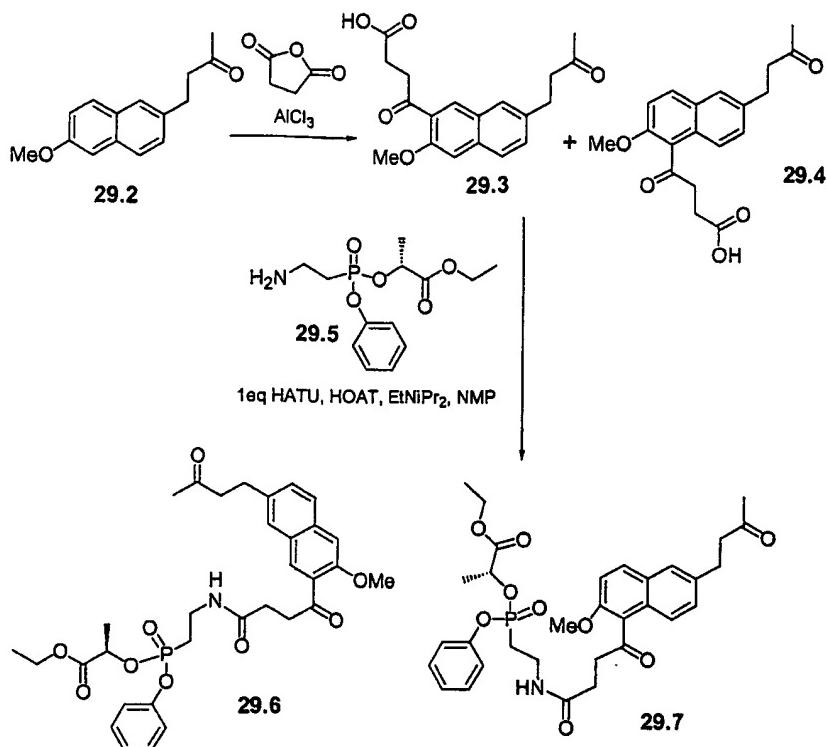
1 minute to 4 hours. To this mixture is added triflate **28.3**. After standard work-up and purification, **28.4** is formed.

Example 29. Synthesis of Representative Compounds of the Invention**29.1**

Representative compounds of the invention (29.1) are illustrated above.

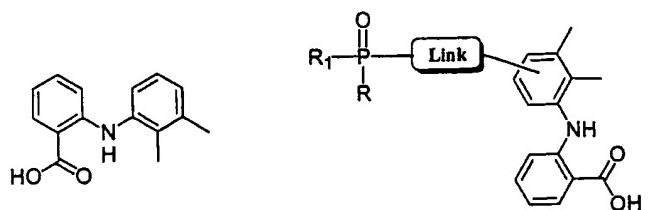
A linkage group is a portion of the structure that links two substructures, one of which is Relafen having the general formula above, the other a phosphonate moiety bearing the appropriate R and R₁ groups. The linkage has at least one uninterrupted chain of atoms other than hydrogen. The R and R₁ groups can be both natural and un-natural amino acid esters linked through the amine nitrogen, or alternatively, one of the groups can be substituted for oxygen linked aryl, alkyl, aralkyl group. Alternatively one of the groups may be an oxygen linked aryl, alkyl, aralkyl group and the other lactate ester.

The preparation of a representative compound of the invention is illustrated below.



Relafen (29.2, US4,106,179), commercially available from Sigm-Aldrich, is converted to carboxylic acids 29.3 and 29.4 by the action of succinic anhydride in the presence of aluminum trichloride in a suitable solvent such as 5 carbon disulfide, nitrobenzene, and dichloroethane. Conversion 29.3 and 29.4 to phosphonate prodrugs occurs by the addition of 1.5 equivalents HOAT, HATU, and diisopropylethylamine to 29.3 and 29.4 followed by the addition of 29.5 all in a suitable solvent such as NMP, DMF, THF, or dichloroethane. This process can either occur after separation of 29.3 from 29.4 by standard means or on the 10 mixture of products. Separation of the final mixture leads to the desired materials. 29.6 and 29.7.

Example 30. Synthesis of Representative Compounds of the Invention

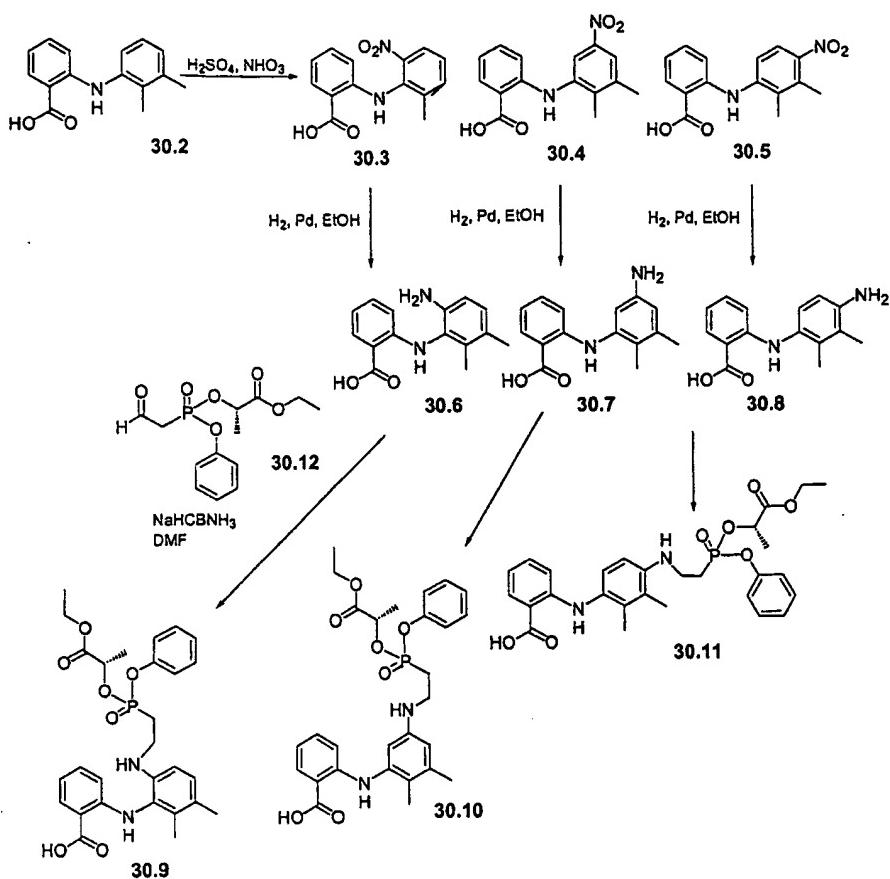


30.1

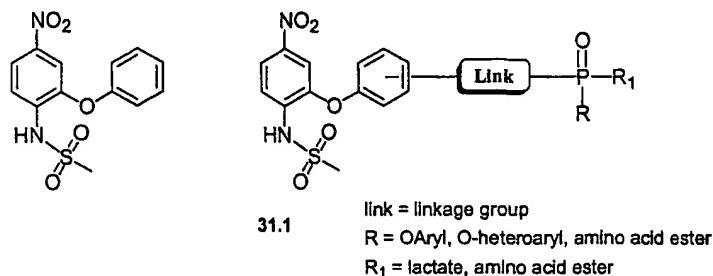
Representative compounds of the invention (30.1) are illustrated above.

- 5 A linkage group is a portion of the structure that links two substructures, one of which is Mefeamic Acid having the general formula above, the other a phosphonate moiety bearing the appropriate R and R₁ groups. The linkage has at least one uninterrupted chain of atoms other than hydrogen. The R and R₁ groups can be both natural and un-natural amino acid esters linked through the
- 10 amine nitrogen, or alternatively, one of the groups can be substituted for oxygen linked aryl, alkyl, aralkyl group. Alternatively one of the groups may be an oxygen linked aryl, alkyl, aralkyl group and the other lactate ester.

The preparation of a representative compound of the invention is illustrated below.

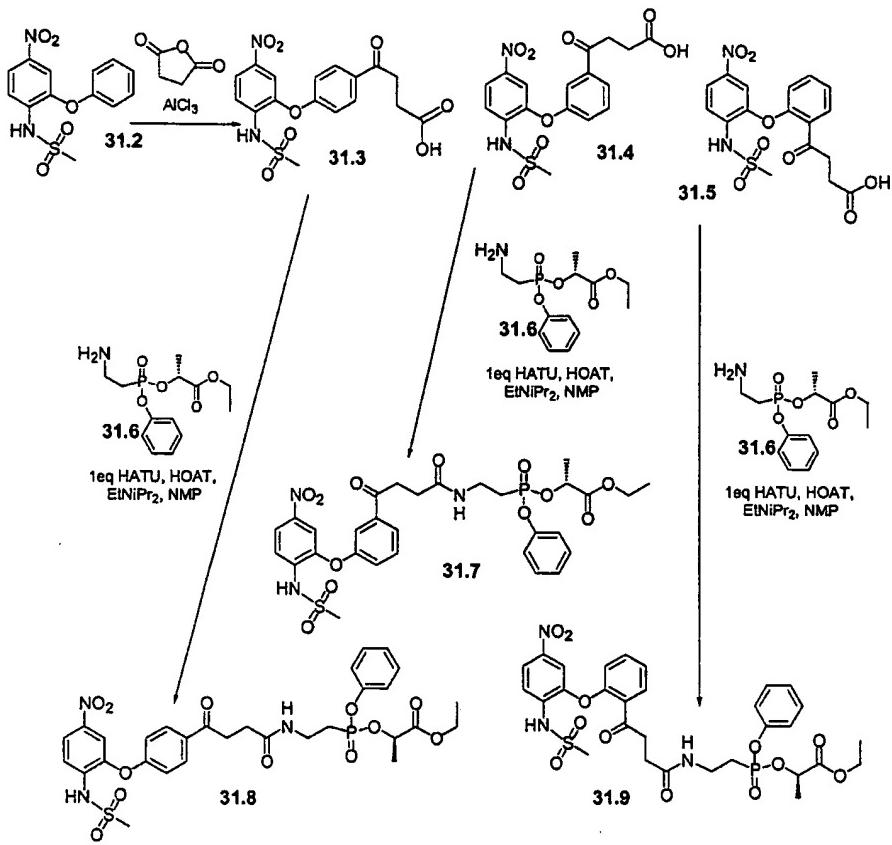


- Mefeamic Acid (30.2, US3,138,636), available from Sigma-Aldrich, is converted to nitro derivatives 30.3, 30.4, and 30.5 by the action of nitric acid in the presence of fuming sulfuric acid. Conversion of 30.3, 30.4, and 30.5 to the corresponding anilines (30.6, 30.7, and 30.8) is performed by reductive amination with 30.12 under a variety of conditions (Zn/AcOH, SnCl₂, H₂/Pd/C) in the appropriate solvents. The anilines are converted to 30.9, 30.10, and 30.11 by the action of a suitable reducing agent (NaCNBH₃, NaHB(OAc)₃, or NaBH₄) all in a suitable solvents such as NMP, DMF, THF, EtOH or dichloroethane.
- 5 The regioisomers can be separated using standard methods known in the art at the nitro, aniline, or phosphonate stages.
- 10 The regioisomers can be separated using standard methods known in the art at the nitro, aniline, or phosphonate stages.

Example 31. Synthesis of Representative Compounds of the Invention

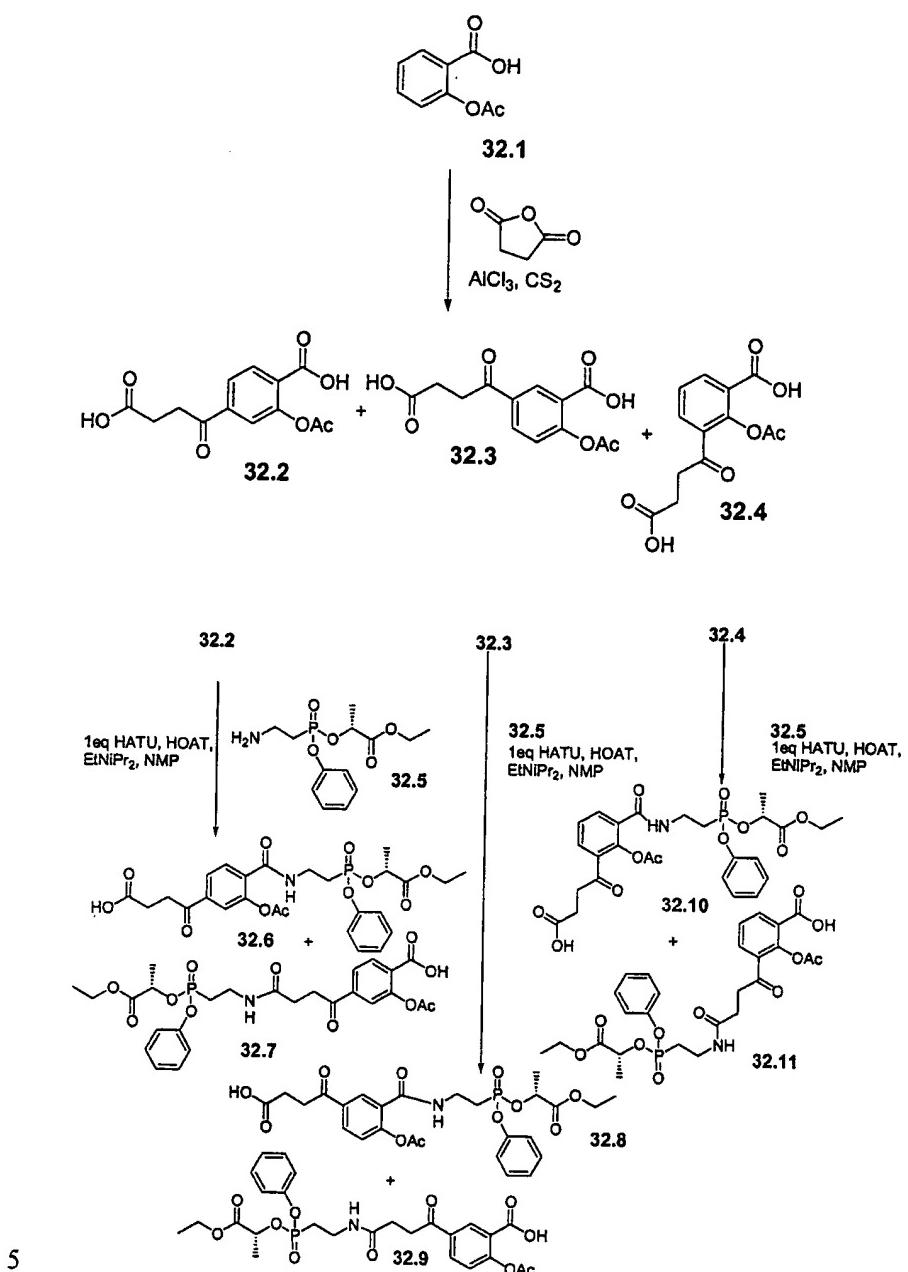
5 Representative compounds of the invention (31.1) are illustrated above.
 A linkage group is a portion of the structure that links two substructures, one of
 which is Nimesulide having the general formula above, the other a phosphonate
 moiety bearing the appropriate R and R₁ groups. The linkage has at least one
 uninterrupted chain of atoms other than hydrogen. The R and R₁ groups can be
 10 both natural and un-natural amino acid esters linked through the amine nitrogen,
 or alternatively, one of the groups can be substituted for oxygen linked aryl,
 alkyl, aralkyl group. Alternatively one of the groups may be an oxygen linked
 aryl, alkyl, aralkyl group and the other lactate ester.

15 The preparation of a representative compound of the invention is
 illustrated below.



- Nimesulide (31.2, US 3,840,597), available from Sigm-Aldrich, is converted to dicarboxylic acids 31.3, 31.4, and 31.5 by the action of succinic anhydride in the presence of a Lewis acid such as aluminum trichloride in a suitable solvent such as carbon disulfide, nitrobenzene, and dichloroethane. The products are separated by standard methods or carried through to the next step after work-up. Conversion of 31.3, 31.4, and 31.5 to phosphonate prodrugs occurs by the addition of 1.5 equivalents HOAT, HATU, and diisopropylethylamine to 31.3, 31.4, and 31.5 followed by the addition of 31.6 all in a suitable solvent such as NMP, DMF, THF, or dichloroethane. Separation and/or purification of the final mixture produces to the desired materials 31.7, 31.8, and 31.9.

Example 32. Synthesis of Representative Compounds of the Invention



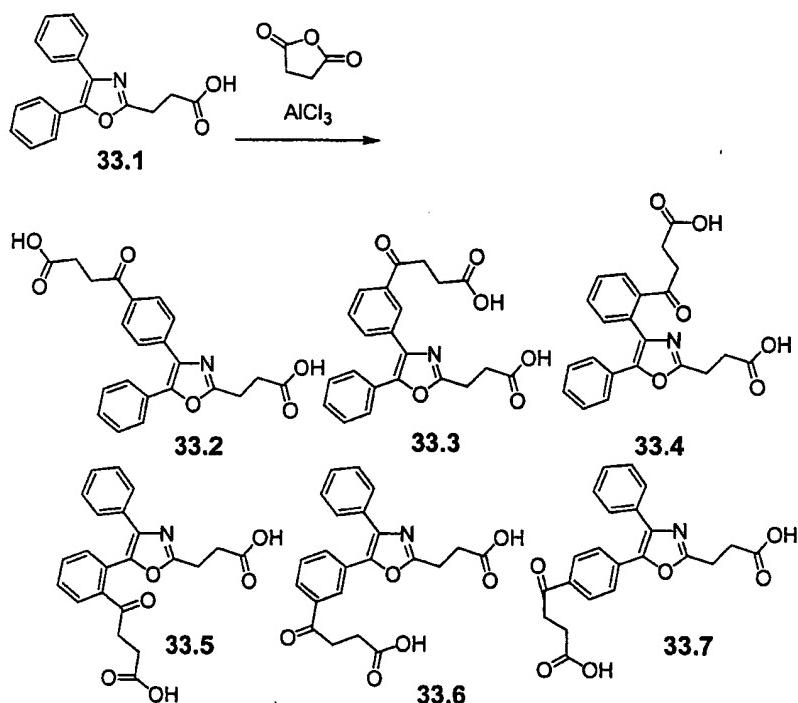
5

Aspirin (32.1), available from Sigma-Aldrich, is converted to dicarboxylic acids 32.2, 32.3, and 32.4 by the action of succinic anhydride in the presence of a Lewis acid such as aluminum trichloride in a suitable solvent (carbon disulfide, nitrobenzene, dichloroethane). Conversion 32.2, 32.3, and

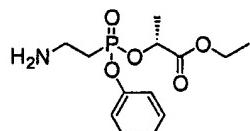
32.4 to phosphonate prodrugs occurs by the addition of 1.5 equivalents HOAT, HATU, diisopropylethylamine to 32.2, 32.3, and 32.4 followed by the addition of 32.5 all in a suitable solvent such as NMP, DMF, THF, or dichloroethane. Separation using standard methods of the final mixture leads to the desired materials 32.6, 32.7, and 32.8, 32.9, 32.10, and 32.11. Alternatively, 3.1, 3.2, and 3.3 can be separated using standard methods and carried forward.

Example 33. Synthesis of Representative Compounds of the Invention

10

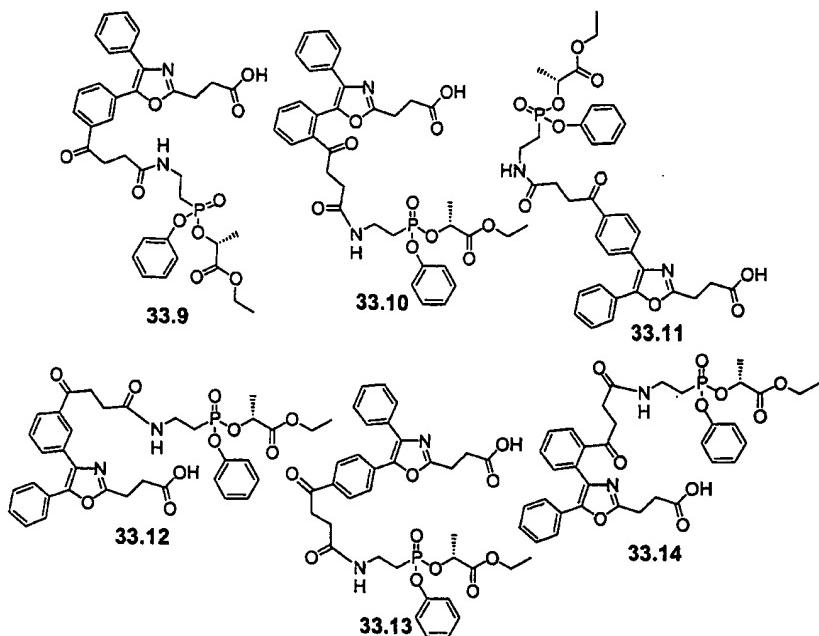


Separate and react each with:

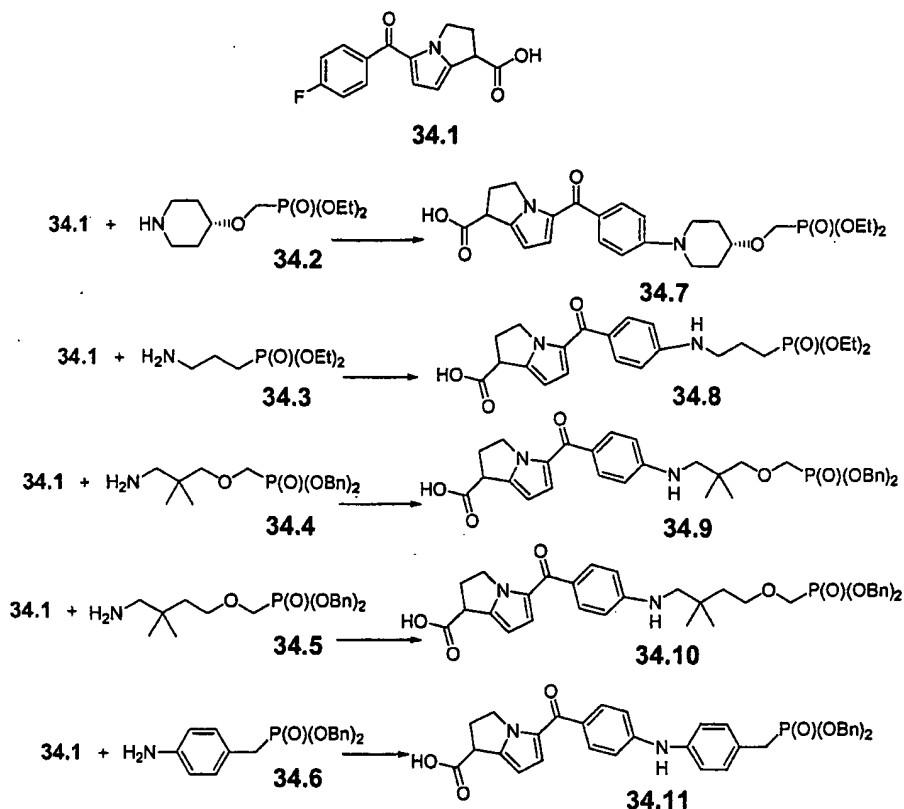


33.8

1.5 eq HATU, HOAT, EtNPr_2 , NMP



Oxaprozin (33.1, US3,578,671), available from Sigma-Aldrich, is converted to carboxylic acids 33.2, 33.3, 33.4, 33.5, 33.6, and 33.7 by the action of succinic anhydride in the presence of a Lewis acid such as aluminum trichloride in a suitable solvent such as carbon disulfide, nitrobenzene, or dichloroethane. Conversion 33.2, 33.3, 33.4, 33.5, 33.6, and 33.7 to phosphonate prodrugs occurs by the addition of 1.5 equivalents HOAT, HATU, and diisopropylethylamine 33.2, 33.3, 33.4, 33.5, 33.6, and 33.7 followed by the addition of 33.8 all in a suitable solvent such as NMP, DMF, THF, or dichloroethane. This process can either occur after separation of 33.2, 33.3, 33.4, 33.5, 33.6, and 33.7 by standard means or on the mixture of products. Separation of the final mixture leads to the desired materials 33.9, 33.10, 33.11, 33.12, 33.13, and 33.14.

Example 34. Synthesis of Representative Compounds of the Invention

- 5 Starting material 34.1 (U.S. Patent 4,347,186) is combined separately with amino phosphonates 34.2, 34.3, 34.4, 34.5, and 34.6 by the action a weak base (for example, diisopropyl ethyl amine, triethyl amine, potassium carbonate, sodium carbonate) in a suitable polar solvent such NMP, DMF, or DMSO and heated between 40 and 200 °C for a period between 30 minutes and 2 weeks.
- 10 Products are isolated and purified using standard protocols. Single enantiomers of 34.7, 34.8, 34.9, 34.10, and 34.11 can be prepared as set out in US4,089,969, page 19 paragraph 10. These resolved intermediates can be carried through as with the linked Toradol compounds to form linked forms of (R)-Ketorolac. Alternatively, resolution of the enantiomers can occur at the 34.2, 34.3, 34.4, 34.5, and 34.6 stage in analogy to US4,089,969.
- 15

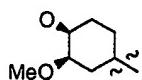
Example 35. Synthesis of Representative Compounds of the Invention

Representative phosphonate compounds can be also be prepared from the compounds described by J.H. Fried et al., *J. Am. Chem. Soc.*, 1963, 85, 236-238 and R. Hirschmann et al., *J. Am. Chem. Soc.*, 1964, 86, 1521-1527 using techniques similar to those described herein.

5

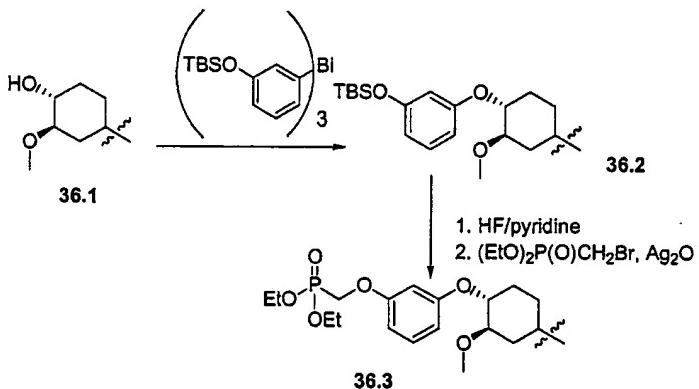
Example 36 Synthesis of Representative Pimecrolimus Analogs of the Invention

In the following illustration the chloro substituted ring of pimecrolimus is replaced by the group



10

and the remainder of the molecule is not shown in the illustration, although it is understood that the remainder of the molecule is present.



15

Ascomycin, a synthetic precursor of pimecrolimus, is *O*-arylated as shown above using an appropriate aryl bismuth reagent according to a procedure such as that reported in *Bioorg. Med. Chem. Lett.*, 1995, 5, 1035. 3-(Dimethyl-*t*-butylsilyloxy)bromobenzene is treated either with magnesium in diethyl ether or with butyllithium in tetrahydrofuran, and the resulting organometallic reagent is reacted with bismuth trichloride to generate the triarybismuthine. After treating with 1 – 1.2 equivalents of peracetic acid, the bismuth(V) reagent is mixed with ascomycin and copper(II) acetate. The reaction is allowed to proceed for a day at room temperature or, if necessary, at reflux, affording the desired 3-(dimethyl-*t*-butylsilyloxy)phenyl ether. After removal of the dimethyl-*t*-butylsilyl

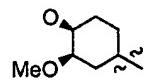
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protecting group, *O*-alkylation is achieved with diethyl (bromomethyl)phosphonate in the presence of silver oxide, affording the desired pimecrolimus analog containing a diethylphosphonate 36.3. Silver ion-assisted reactions have been used to mediate *O*-alkylations of ascomycin: see *J. Med. Chem.*, 1998, 41, 1764.

5 *Chem.*, 1998, 41, 1764.

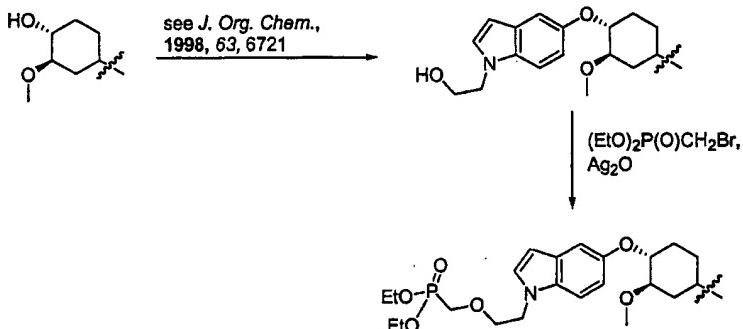
Example 37 Synthesis of Representative Pimecrolimus Analogs of the Invention

In the following illustration the chloro substituted ring of pimecrolimus is replaced by the group



10

and the remainder of the molecule is not shown in the illustration, although it is understood that the remainder of the molecule is present.

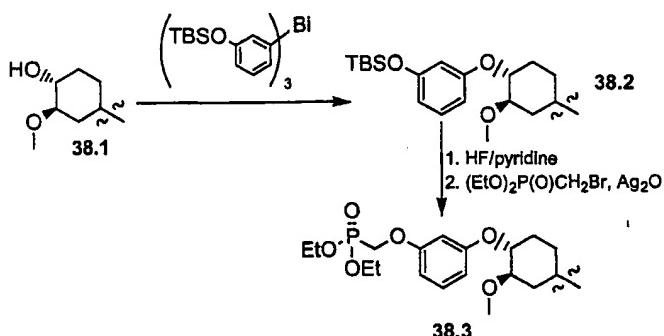


15

A phosphonate derivative of pimecrolimus indolyl ether is prepared as illustrated above, in a similar manner to that described in Example 36, with the exception that the key triindolylbismuthine intermediate is obtained from 5-bromoindole following the procedure described in *J. Org. Chem.* 1998, 63, 6721.

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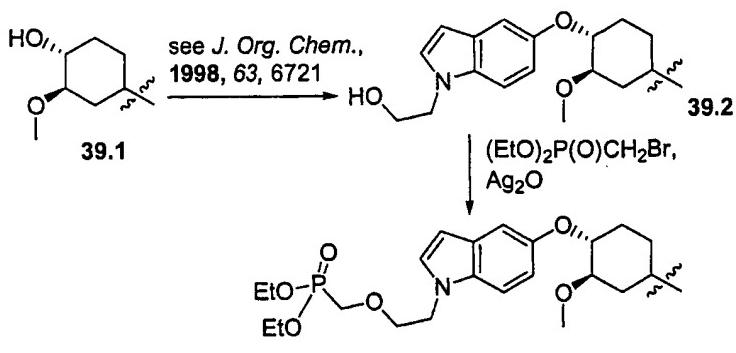
Example 38 Synthesis of Representative Everolimus Analogs of the Invention



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- Rapamycin (compound 38.1 wherein the remaining portion of the rapamycin structure is not shown), a synthetic precursor of everolimus, is *O*-arylated as shown above using an appropriate aryl bismuth reagent according to a procedure such as that reported in *Bioorg. Med. Chem. Lett.*, 1995, 5, 1035.
- 10 (Dimethyl-*t*-butylsilyloxy)bromobenzene is treated either with magnesium in diethyl ether or with butyllithium in tetrahydrofuran, and the resulting organometallic reagent is reacted with bismuth trichloride to generate the triarylbismuthine. After treating with 1 – 1.2 equivalents of peracetic acid, the bismuth(V) reagent is mixed with rapamycin and copper(II) acetate. The reaction is allowed to proceed for a day at room temperature or, if necessary, at reflux, affording the desired 3-(dimethyl-*t*-butylsilyloxy)phenyl ether 38.2. After removal of the dimethyl-*t*-butylsilyl protecting group, *O*-alkylation is achieved with diethyl (bromomethyl)phosphonate in the presence of silver oxide, affording the desired everolimus analog containing the diethylphosphonate 38.3.
- 15 Silver ion-assisted reactions have been used to mediate *O*-alkylations on an immunosuppressive macrolide structurally similar to rapamycin: see *J. Med. Chem.*, 1998, 41, 1764.
- 20

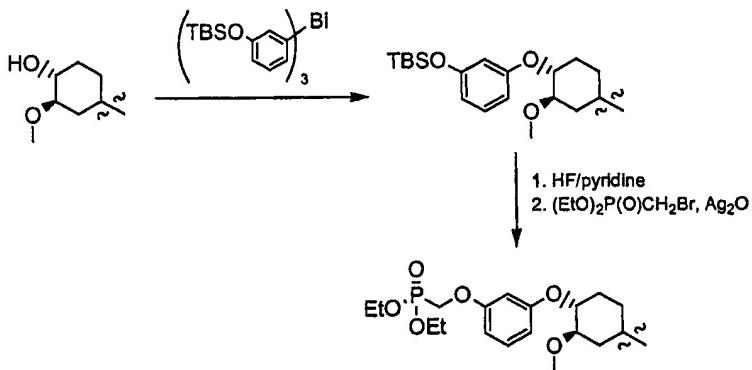
Example 39 Synthesis of Representative Everolimus Analogs of the Invention



5

A phosphonate derivative of everolimus indolyl ether is prepared from rapamycin (formula 39.1 wherein the remaining portion of the rapamycin structure is not shown) in a similar manner to that described in Example 38, with the exception that the key triindolylbismuthine intermediate is obtained from 5-bromoindole following the procedure described in *J. Org. Chem.* 1998, 63, 6721.

Example 40 Synthesis of Representative Sirolimus Analogs of the Invention



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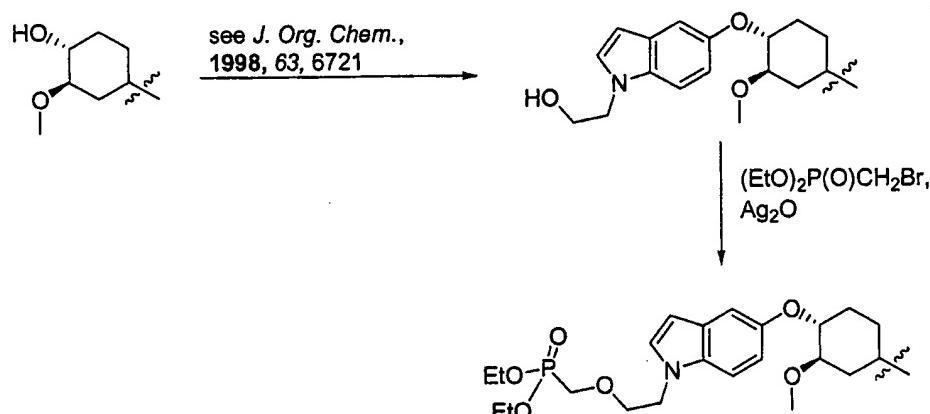
Sirolimus is *O*-arylated as shown above using an appropriate aryl bismuth reagent according to a procedure such as that reported in *Bioorg. Med. Chem. Lett.*, 1995, 5, 1035. 3-(Dimethyl-*t*-butylsilyloxy)bromobenzene is treated either with magnesium in diethyl ether or with butyllithium in tetrahydrofuran, and the resulting organometallic reagent is reacted with bismuth

trichloride to generate the triarylbismuthine. After treating with 1 – 1.2 equivalents of peracetic acid, the bismuth(V) reagent is then mixed with sirolimus and copper(II) acetate. The reaction is allowed to proceed for a day at room temperature or, if necessary, at reflux, affording the desired 3-(dimethyl-t-butylsilyloxy)phenyl ether. After removal of the dimethyl-t-butylsilyl protecting group, *O*-alkylation is achieved with diethyl (bromomethyl)phosphonate in the presence of silver oxide, affording the desired sirolimus analog containing the diethylphosphonate. Silver ion-assisted reactions have been used to mediate *O*-alkylations on an immunosuppressive macrolide structurally similar to sirolimus:

5 see *J. Med. Chem.*, 1998, 41, 1764.

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Example 41 Synthesis of Representative Sirolimus Analogs of the Invention

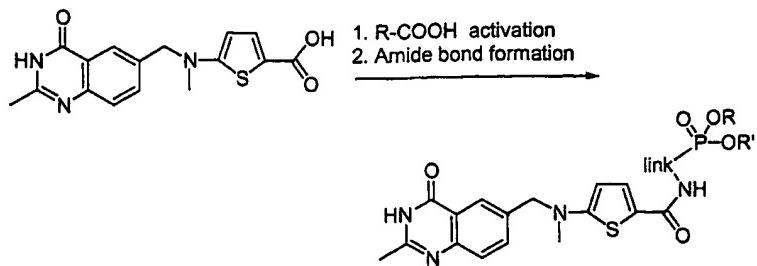


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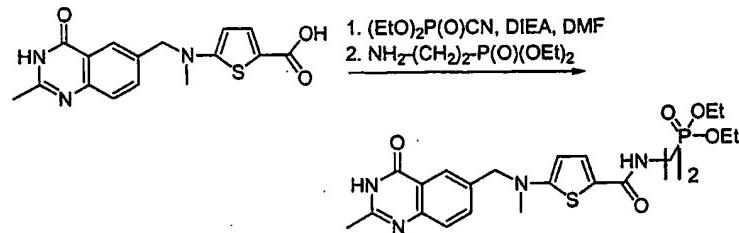
A sirolimus indolyl ether is prepared as illustrated above, in a similar manner to that described in Example 40, with the exception that the key triindolylbismuthine intermediate is obtained from 5-bromoindole following the procedure described in *J. Org. Chem.* 1998, 63, 6721.

20

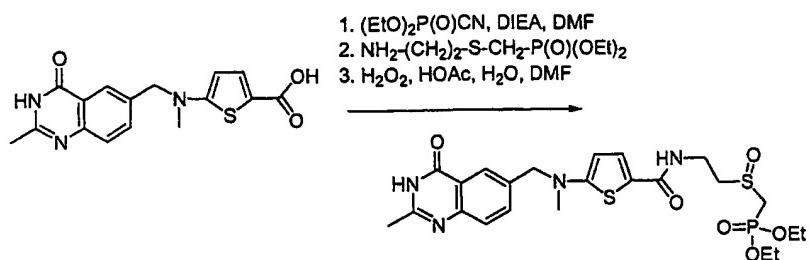
Example 42. Synthesis of Representative Compounds of the Invention



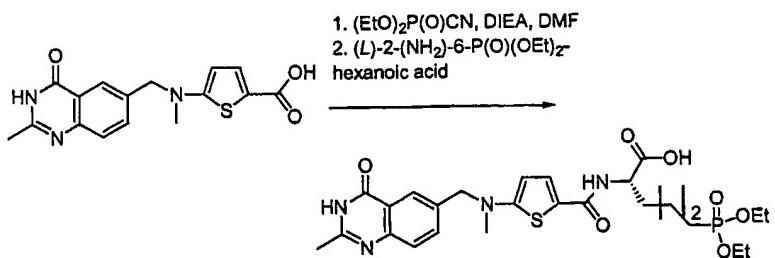
Representative compounds of the invention can be prepared as illustrated above. The preparation of a specific compound of the invention is described 5 below.



The starting carboxylic acid can be treated in a solvent such as dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP) with a coupling 10 reagent such as diethyl cyanophosphonate or *isobutyl* chloroformate and a base such as diisopropylethylamine (DIEA) at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation is complete, 2-aminoethylphosphonic acid diethyl ester (commercially available) 15 is added. After consumption of the activated species is observed the solvent is removed in vacuo and the product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like.

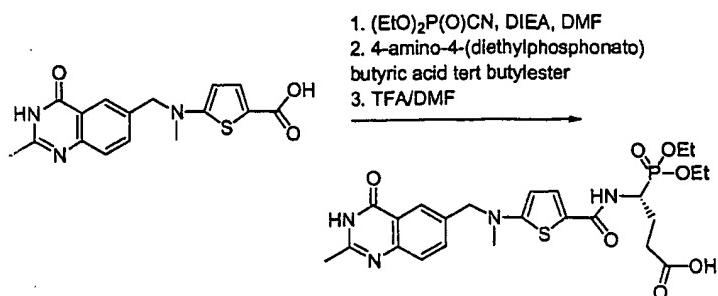
Example 43. Synthesis of Representative Compounds of the Invention

- 5 The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as diisopropylethylamine (DIEA) at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation is complete, (2-amino-ethylsulfanylmethyl)-
- 10 phosphonic acid diethyl ester (made by base-catalyzed coupling of 2-aminoethanethiol with diethyl phosphonomethyltriflate, prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the intermediate is isolated via chromatography. Alternatively, the intermediate can be isolated
- 15 through precipitation from the reaction solution with an organic solvent like diethyl ether or the like. The intermediate is then dissolved in a mixture of water, DMF, and acetic acid and is treated with hydrogen peroxide solution (excess). After removal of the solvents the product is isolated via chromatography.
- 20 Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like.

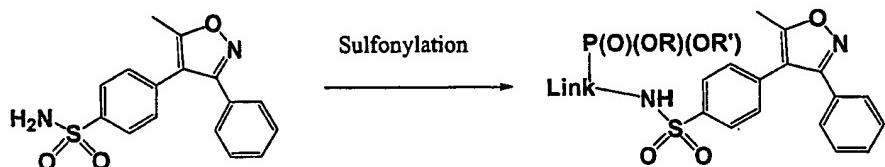
Example 44. Synthesis of Representative Compounds of the Invention

The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as DIEA at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604.). When the activation is complete, (*L*)-2-amino-6-(diethylphosphonato)-hexanoic acid is added. After consumption of the activated species is observed the solvent is removed in vacuo and the product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like.

10

Example 45. Synthesis of Representative Compounds of the Invention

- 5 The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as DIEA at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation is complete, 4-amino-4-(diethylphosphonato)-butyric acid tert butylester (*J. Am. Chem. Soc.*, 1995, 117, 10879-10888) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the intermediate is isolated via chromatography. Alternatively, the intermediate can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like. The crude intermediate is then dissolved in
- 10 ~~DMF~~ and treated with trifluoroacetic acid (TFA). The product is isolated via chromatography after removal of the solvents. Alternatively, the product can be isolated through precipitation form the reaction solution with an organic solvent like diethyl ether or the like.
- 15 ~~DMF~~ and treated with trifluoroacetic acid (TFA). The product is isolated via chromatography after removal of the solvents. Alternatively, the product can be isolated through precipitation form the reaction solution with an organic solvent like diethyl ether or the like.

Example 46. Synthesis of Representative Compounds of the Invention

- 20 Representative compounds of the invention can be prepared as illustrated above. Sulfenylation is conveniently carried out by reaction of the aniline with a sulfonyl chloride in the presence of a base such as triethylamine (*J. Med. Chem.*, 1995, 38, 4897) in a solvent such as dichloromethane. Either one equivalent or
- 25 two equivalents of the sulfonyl chloride are used.

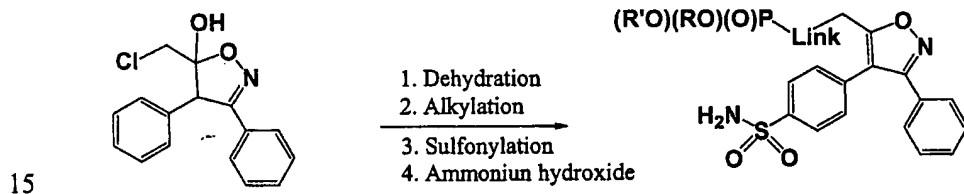
an excess of the sulfonyl chloride may be used; in the latter case, the bis-sulfonamide may be formed, in which case hydrolysis to the monosulfonamide is achieved through reaction with sodium hydroxide.

A sulfonylating reagent that can be used in the above procedure can be
5 prepared as follows.



(3-Bromo-propyl)-phosphonic acid diethyl ester is treated with sodium sulfide in a solvent such as ethanol, and the thiol produced is oxidized with 10 chlorine in an aqueous solvent system to give the sulfonyl chloride (see Gilbert, 'Sulfonylation and Related Reactions, Interscience, New York, 1965, pp 202-214).

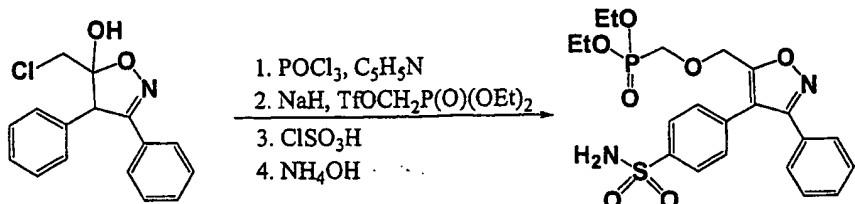
Example 47. Synthesis of Representative Compounds of the Invention



The starting chloromethyl compound (see *J. Med. Chem.*, 2000, 43, 775) serves as a useful intermediate for the introduction of a phosphonate moiety at the methyl substituent of the isoxazole. After this is achieved, the sulfonamide group is introduced by the same methods as for valdecoxib itself.
20

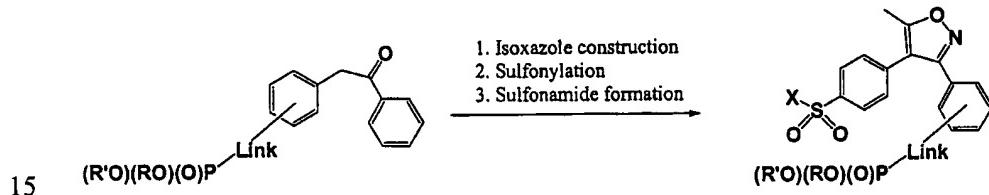
Optionally, the parecoxib-style prodrug may be formed by acylation of the sulfonamide using propionic anhydride and a base such as triethylamine, followed by formation of the sodium salt with sodium hydroxide (see *J. Med. Chem.*, 2000, 43, 1661).

25 A representative compound of the invention can be prepared as follows.



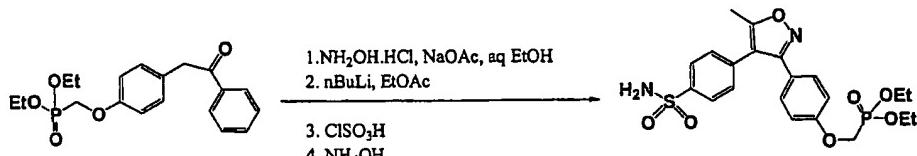
The chloromethyl compound (see *J. Med. Chem.*, 2000, 43, 775) is treated with a dehydrating reagent such as phosphorus oxychloride in the presence of a base such as pyridine, optionally in a solvent such as dichloromethane. The (5-chloromethyl)isoxazole so formed is then treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added, yielding the desired phosphonate diester. Sulfenylation with chlorosulfonic acid, quenching the resulting sulfonyl chloride with ammonium hydroxide (according to *J. Med. Chem.*, 2000, 43, 775) gives the desired product.

Example 48. Synthesis of Representative Compounds of the Invention



Representative compounds of the invention can also be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

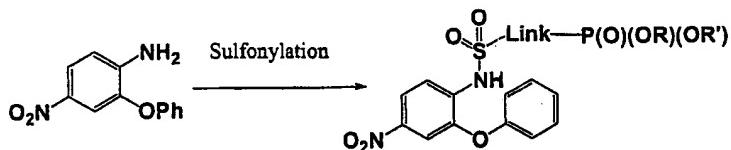
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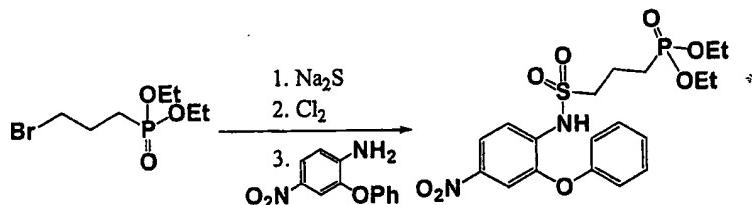
The deoxybenzoin derivative bearing a phosphonate moiety (formed from commercially available 2-(4-methoxyphenyl)acetophenone by demethylation

with hydrobromic acid in acetic acid, and subsequent alkylation with diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) in the presence of a base such as potassium carbonate in a solvent such as dimethylformamide) is subjected to the same transformations as those outlined 5 in *J. Med. Chem.*, 2000, 43, 775 to provide the phosphonate compound of the invention.

Example 49. Synthesis of Representative Compounds of the Invention

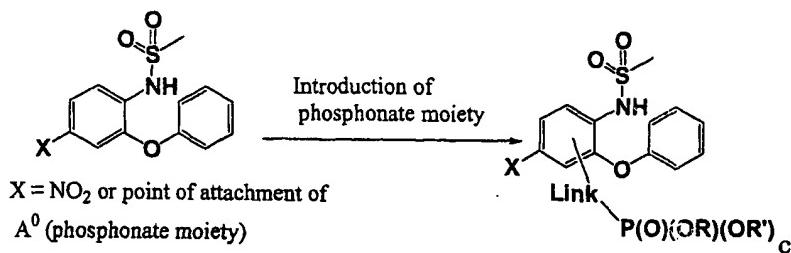


10 Representative compounds of the invention can be prepared as illustrated above. Sulfonylation is conveniently carried out by reaction of the aniline with a sulfonyl chloride in the presence of a base such as triethylamine (*J. Med. Chem.*, 1995, 38, 4897) in a solvent such as dichloromethane. Either one equivalent or an excess of the sulfonyl chloride may be used; in the latter case, the bis- 15 sulfonamide is formed, and hydrolysis to the monosulfonamide is achieved through reaction with sodium hydroxide. For example, a specific compound of the invention can be prepared as follows.



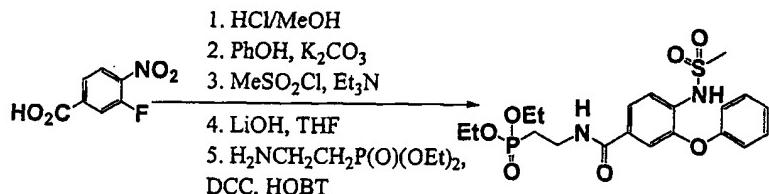
20 (3-Bromo-propyl)-phosphonic acid diethyl ester is treated with sodium sulfide in a solvent such as ethanol, and the thiol produced is oxidised with chlorine in an aqueous solvent system to give the sulfonyl chloride (see Gilbert, 'Sulfonylation and Related Reactions, Interscience, New York, 1965, pp 202-214). This reagent is used in the sulfonylation reaction described above to provide the representative compound of the invention.

Example 50. Synthesis of Representative Compounds of the Invention



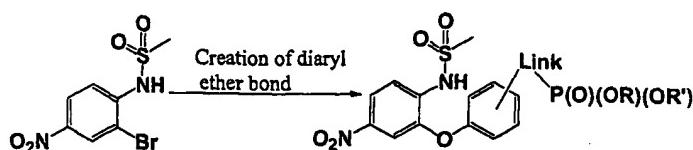
Representative compounds of the invention can be prepared as illustrated above. The phosphonate moiety may be attached to the central phenyl ring. If it is linked at the position para- to the sulfonylamide residue, the linker should optimally exert an electron-withdrawing effect to maximize the COX-2 inhibitory activity (see *J. Med. Chem.*, 1995, 38, 4897). For example, a specific compound of the invention can be prepared as follows.

10



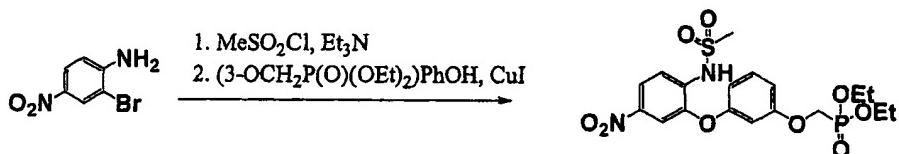
3-Fluoro-4-nitrobenzoic acid is esterified by heating briefly in acidic methanol. Treatment with phenol in a solvent such as dimethylformamide in the presence of a base such as potassium carbonate causes displacement of the fluoride and generation of the bis-aryl ether. Subsequent saponification of the benzoate ester with lithium hydroxide in a solvent such as tetrahydrofuran gives the free acid, which is coupled with 2-aminoethylphosphonic acid diethyl ester (commercially available) using standard reagents for the formation of a secondary amide such as dicyclohexylcarbodiimide (DCC) and hydroxybenztriazole (HOBT), in a solvent such as dimethylformamide.

Example 51. Synthesis of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. The diaryl ether is conveniently formed using the Ullman method (*Russ. Chem. Rev.*, 1974, 43, 679), catalyzed by copper (I) salts. Using this method, a phenol already bearing a phosphonate moiety may be used to generate the desired analog efficiently. For example, a specific compound of the invention can be prepared as follows.

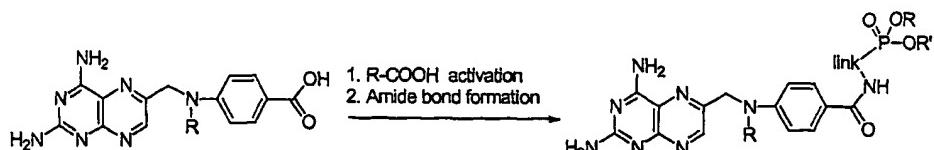
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2-Bromo-4-nitroaniline is sulfonylated in a manner similar to that described in example 49. The subsequent Ullman ether synthesis using (3-hydroxy-phenoxyethyl)phosphonic acid diethyl ester (formed by the reaction of resorcinol and diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) in the presence of a base such as magnesium t-butoxide gives the desired product.

Example 52. Synthesis of Representative Compounds of the Invention

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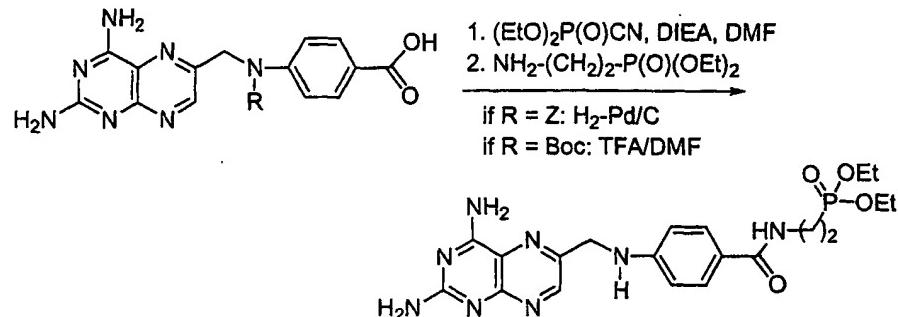


Representative compounds of the invention can be prepared as illustrated above. Final compounds, be they diastereoisomers or enantiomers, may typically be purified by chromatographic means. In case a direct coupling to aminopterin is hampered by the presence of a free secondary amine in the

starting material ($R = H$), this entity is temporarily protected either with a tert.butoxycarbonylgroup ($R = Boc$) or benzyloxycarbonyl ($R = Cbz$ or Z) according to standard procedures (Green Wutts: Protective groups in organic chemistry)

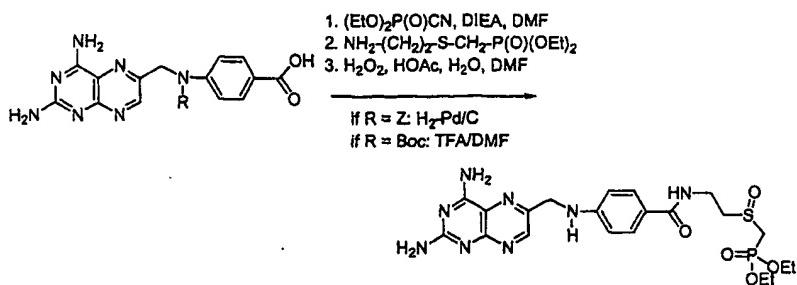
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Example 53. Synthesis of Representative Compounds of the Invention



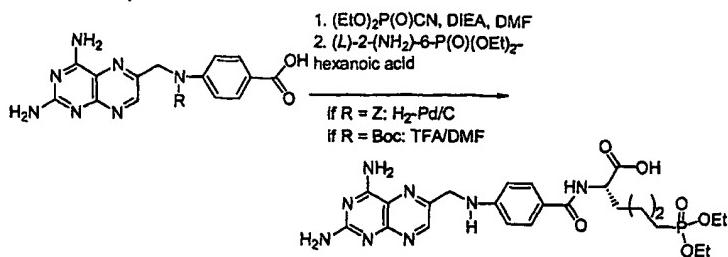
- 10 The starting carboxylic acid can be treated in a solvent such as dimethylformamide (DMF) or N-methylpyrrolidinone (NMP) with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as diisopropylethylamine (DIEA) at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation 15 is complete, 2-aminoethylphosphonic acid diethyl ester (commercially available) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent such as diethyl ether or the like.
- 20 In case $R = Z$: The compound is dissolved in an organic solvent like DMF or NMP and a catalytic amount of Pd/C is added. The reaction mixture is stirred under an atmosphere of hydrogen until the starting material is consumed. The Pd/C is removed by filtration and the solvent is evaporated in vacuo. The product is isolated via chromatography. Alternatively, the product can be 25 isolated through precipitation from the reaction solution with an organic solvent such as diethyl ether or the like.

Example 54. Synthesis of Representative Compounds of the Invention



5 The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as diisopropylethylamine (DIEA) at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation is complete, (2-amino-ethylsulfanylmethyl)-
 10 phosphonic acid diethyl ester (made by base-catalyzed coupling of 2-aminoethanethiol with diethyl phosphonomethyltriflate, prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the intermediate is isolated via chromatography. Alternatively, the intermediate can be isolated
 15 through precipitation from the reaction solution with an organic solvent like diethyl ether or the like. The intermediate is then dissolved in a mixture of water, DMF, and acetic acid and is treated with hydrogen peroxide solution (excess). After removal of the solvents the product is isolated via chromatography.
 Alternatively, the product can be isolated through precipitation from the reaction
 20 solution with an organic solvent like diethyl ether or the like.

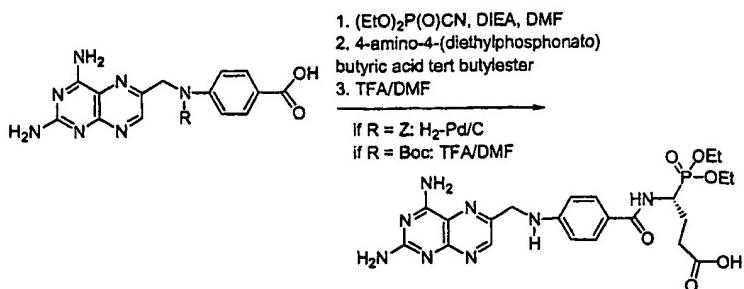
In case $\text{R} = \text{Z}$: The compound is dissolved in an organic solvent like DMF or NMP and a catalytic amount of Pd/C is added. The reaction mixture is stirred under an atmosphere of hydrogen until the starting material is consumed. The Pd/C is removed by filtration and the solvent is evaporated in vacuo. The
 25 product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent such as diethyl ether or the like.

Example 55. Synthesis of Representative Compounds of the Invention

5 The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as DIEA at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604.). When the activation is complete, (L)-2-amino-6-(diethylphosphonato)-hexanoic acid is added. After 10 consumption of the activated species is observed the solvent is removed in vacuo and the product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent such as diethyl ether or the like.

In case $\text{R} = \text{Z}$: The compound is dissolved in an organic solvent like 15 DMF or NMP and a catalytic amount of Pd/C is added. The reaction mixture is stirred under an atmosphere of hydrogen until the starting material is consumed. The Pd/C is removed by filtration and the solvent is evaporated in vacuo. The product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent 20 such as diethyl ether or the like.

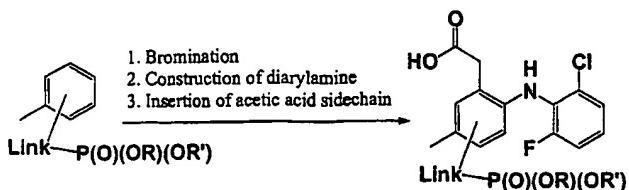
Example 56. Synthesis of Representative Compounds of the Invention



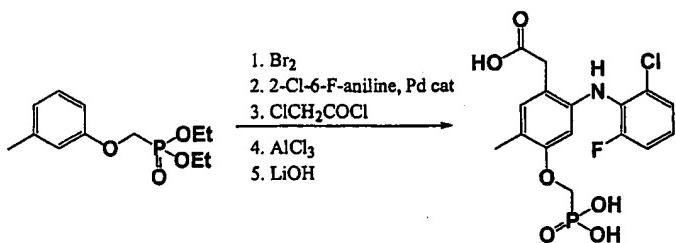
- The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as DIEA at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation is complete, 4-amino-4-(diethylphosphonato)-butyric acid tert butylester (*J. Am. Chem. Soc.*, 1995, 117, 10879-10888) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the intermediate is isolated via chromatography. Alternatively, the intermediate can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like. The crude intermediate is then dissolved in DMF and treated with TFA (excess). The product is isolated via chromatography after removal of the solvents. Alternatively, the product can be isolated through precipitation form the reaction solution with an organic solvent such as diethyl ether or the like.

- In case R = Z: The compound is dissolved in an organic solvent like DMF or NMP and a catalytic amount of Pd/C is added. The reaction mixture is stirred under an atmosphere of hydrogen until the starting material is consumed. The Pd/C is removed and the solvent is evaporated in vacuo. The product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent such as diethyl ether or the like.

25 **Example 57. Synthesis of Representative Compounds of the Invention**

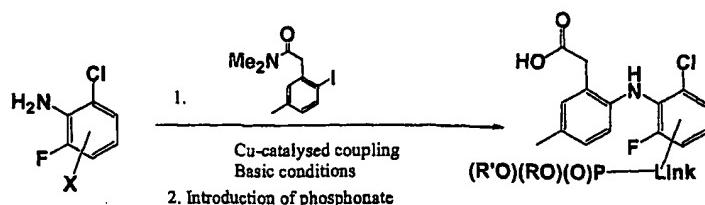


Representative compounds of the invention can be prepared as illustrated above. The construction of the lumiracoxib core proceeds according to the 5 procedures described in WO-00123346. For example, a specific compound of the invention can be prepared as follows.



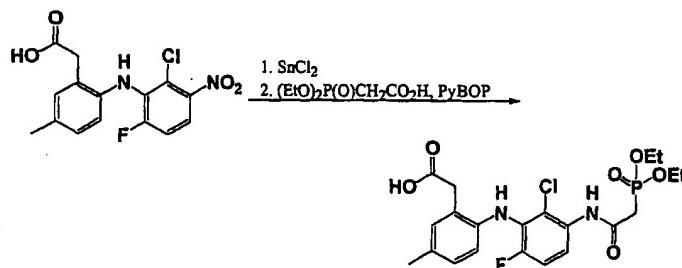
- Bromination (by standard methods – see de la Mare, ‘Electrophilic 10 Halogenation’, Cambridge University Press, London, 1976) of *m*-tolyloxymethylphosphonic acid diethyl ester (formed from commercially available 3-methylphenol by alkylation with diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) in the presence of a base such as potassium carbonate) gives a mixture of isomers that are separated 15 by chromatography, each of which is potentially useful in the synthesis of analogs containing phosphonate moieties linked to different positions of the phenyl ring in question. Subsequent steps proceed as described in WO-00123346, yielding ultimately a phosphonic acid analog of lumiracoxib. The key step is the coupling of the aryl bromide and 2-chloro-5-fluoroaniline, 20 catalyzed by a palladium (II) salt, typically with sodium t-butoxide as base (see *Angew. Chem. Int. Ed.*, 1998, 37, 2046-2067).

Example 58. Synthesis of Representative Compounds of the Invention



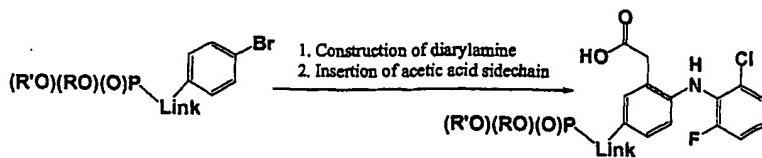
X = group suitable for transformation
to phosphonate moiety

Representative compounds of the invention can be prepared as illustrated above. This route to lumiracoxib analogs is described in WO-09911605, and relies on a copper-catalyzed step for forming the bis-aryl amine with the phenyl acetic acid side chain already in place on one of the reagents. The phosphonate-bearing moiety is conveniently introduced after this step, which typically requires heating (e.g. in xylenes). For example, a specific compound of the invention can be prepared as follows.



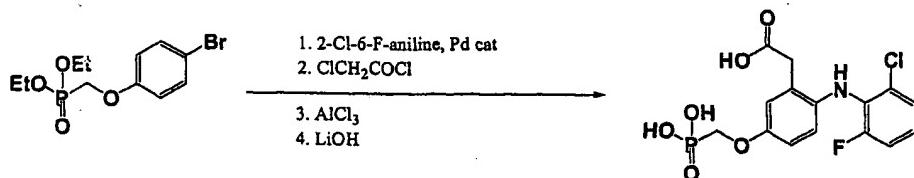
The product of coupling between N,N-dimethyl-5-methyl-2-iodophenylacetamide and 2-chloro-6-fluoro-5-nitroaniline is subjected to reduction under standard conditions such as treatment with tin(II) chloride or hydrogenation over palladium on charcoal. The resulting primary aniline is coupled with (diethoxy-phosphoryl)acetic acid (commercially available) in the presence of a reagent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP®) to provide the compound of the invention.

Example 59. Synthesis of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. This route is analogous to that described in Example 57. A specific compound of the invention can be prepared as follows.

5

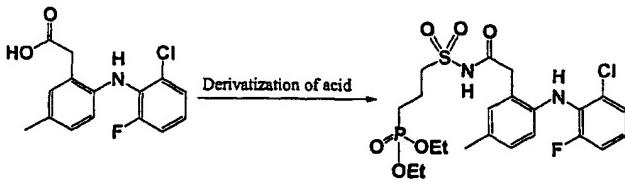


(4-Bromo-phenoxymethyl)phosphonic acid diethyl ester (formed from commercially available 4-bromophenol by alkylation with diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27,

- 10 1477) in the presence of a base such as potassium carbonate) serves a suitable starting material for an analog bearing a phosphonate linked at the position shown, using chemistry analogous to that described in Example 57 above.

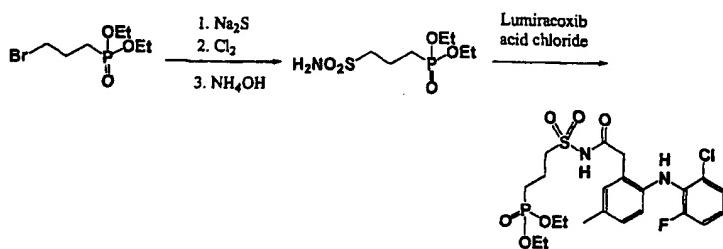
Example 60. Synthesis of Representative Compounds of the Invention

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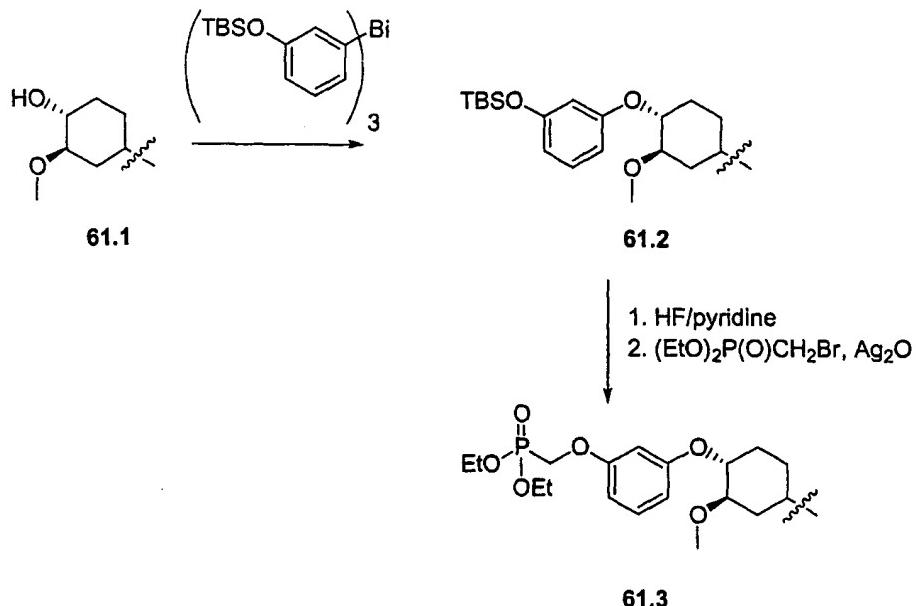
Representative compounds of the invention can be prepared as illustrated above. The phosphonate-bearing moiety may be attached to the carboxylate residue of lumiracoxib using a derivative such as an acylsulfonamide to preserve the acidic nature of the group. For example, a specific compound of the

- 20 invention can be prepared as follows.



(3-Bromo-propyl)-phosphonic acid diethyl ester is treated with sodium sulfide in a solvent such as ethanol, and the thiol produced is oxidized with chlorine in an aqueous solvent system to give the sulfonyl chloride (see Gilbert, 'Sulfonylation and Related Reactions, Interscience, New York, 1965, pp 202-214). This reagent is treated briefly with ammonium hydroxide to generate the sulfonamide, which is condensed with the acid chloride of lumiracoxib (generated by treatment of lumiracoxib with thionyl chloride in a solvent such as diochloromethane), yielding the compound of the invention.

Example 61 Synthesis of Representative Tacrolimus Analogs of the Invention



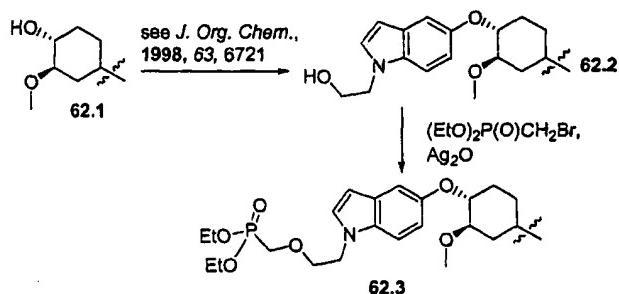
5

Tacrolimus (compound 61.1 wherein the remaining portion of the tacrolimus molecule is not shown) is *O*-arylated as shown above using an appropriate aryl bismuth reagent according to a procedure such as that reported in *Bioorg. Med. Chem. Lett.*, 1995, 5, 1035. 3-(dimethyl-t-butylsilyloxy)bromobenzene is treated either with magnesium in diethyl ether or with butyllithium in tetrahydrofuran, and the resulting organometallic reagent is reacted with bismuth trichloride to generate the triarylbismuthine. After treating with 1 – 1.2 equivalents of peracetic acid, the bismuth(V) reagent is mixed with tacrolimus 61.1 and copper(II) acetate. The reaction is allowed to proceed for a day at room temperature or, if necessary, at reflux, affording the desired 3-(dimethyl-t-butylsilyloxy)phenyl ether. After removal of the dimethyl-t-butylsilyl protecting group with HF, *O*-alkylation is achieved with diethyl (bromomethyl)phosphonate in the presence of silver oxide, affording the desired tacrolimus analog containing the diethylphosphonate 61.3. Silver ion-assisted

reactions have been used to mediate *O*-alkylations on an immunosuppressive macrolide structurally similar to tacrolimus: see *J. Med. Chem.*, 1998, 41, 1764.

Example 62 Synthesis of representative Tacrolimus Analogs of the Invention

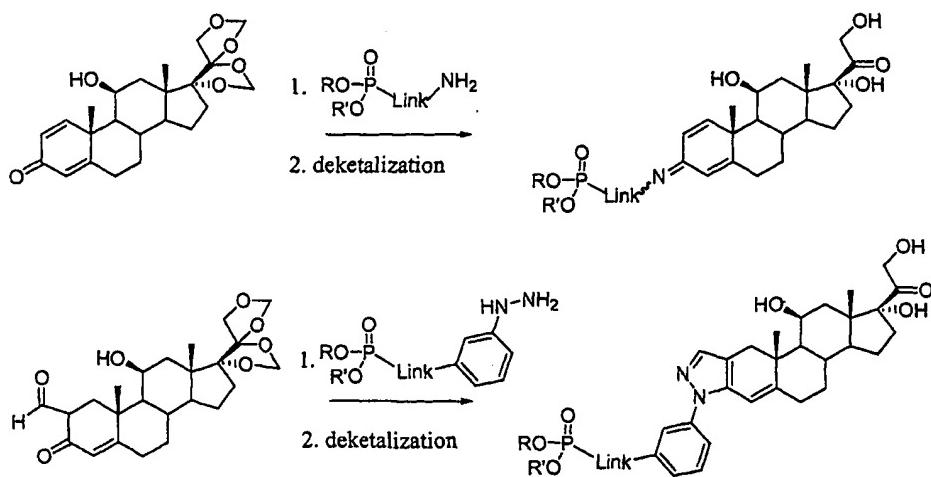
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A phosphonate derivative of tacrolimus indolyl ether is prepared from tacrolimus (compound 62.1 wherein the remaining portion of the tacrolimus molecule is not shown) in a similar manner to that described in Example 61 with the exception that the key triindolylbismuthine intermediate is obtained from 5-bromoindole following the procedure described in *J. Org. Chem.* 1998, 63, 6721.

Example 63 Synthesis of Representative Compounds of the Invention

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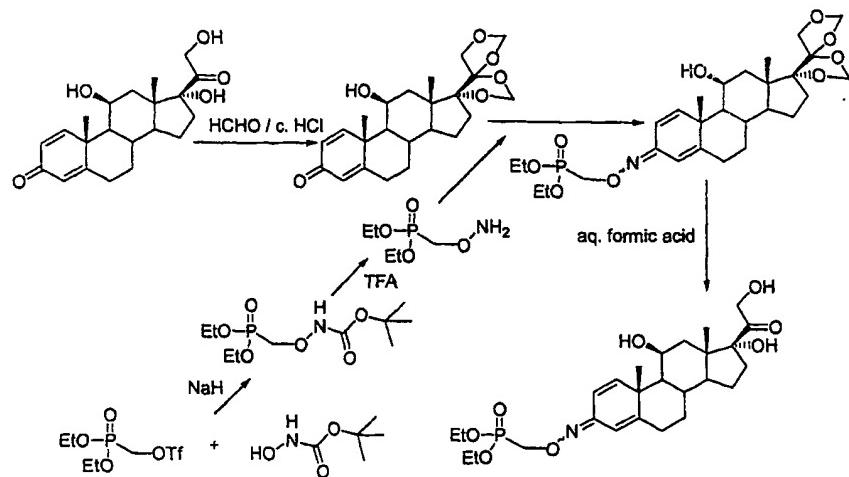


Representative compounds of the invention can be made by procedures such as those described by Boer, et al, *J. Mass Spectrom.* 1995, 30, 497-504 and

Hoyte, et al, *J. Med. Chem.* 2002, 45, 5397-5405, or they can be made according to the general routes outlined above.

Example 64 Synthesis of Representative Compounds of the Invention

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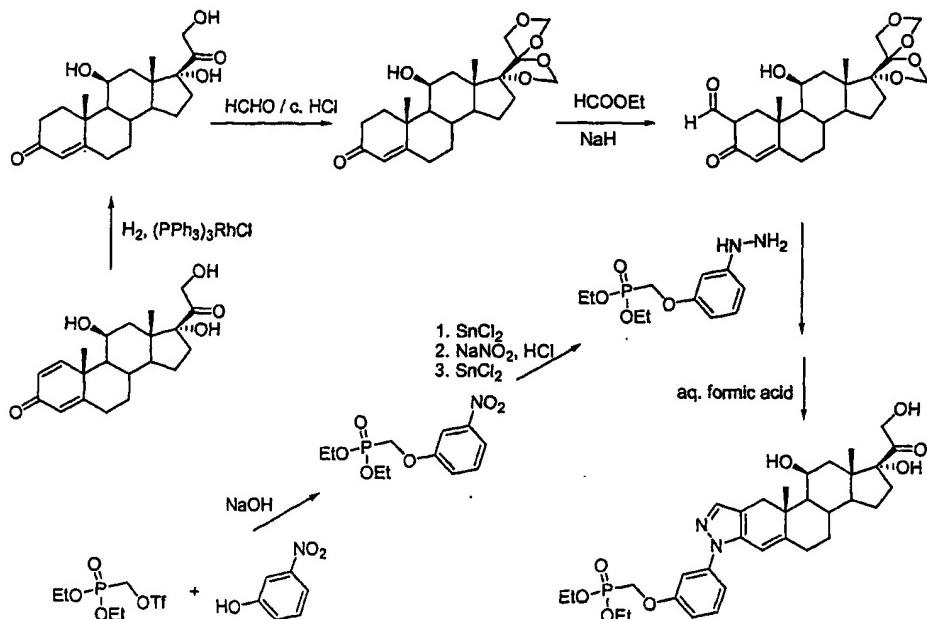


Prednisolone is treated in a solvent such as chloroform with formaldehyde in the presence of an acid such as concentrated hydrochloric acid.

- 10 After stirring for several hours (preferably 7 to 10 hours) at room temperature, the layers are separated and the organic layer is concentrated to afford the bis(methylenedioxy) intermediate (Hirschmann, R. et al, *J. Am. Chem. Soc.* 1964, 86, 1520-1527). This intermediate is treated with diethyl (aminooxymethyl)phosphonate in a solvent such as pyridine to afford the oxime,
- 15 which is then treated with aqueous acid to remove the bis-(methylenedioxy) protecting group. For example, the oxime is treated with 60% aqueous formic acid and heated at 90 °C for 10 min., cooled and concentrated using portions of ethanol to assist in removing formic acid. Chromatographic purification and/or crystallization of the residue yield the phosphonate oxime analog of prednisolone. A key precursor of this synthesis, diethyl (aminooxymethyl)-
- 20 phosphonate, can be obtained from diethyl (trifluoromethylsulfonyloxy)methyl phosphonate and N-(t-butoxycarbonyl)-hydroxylamine. Accordingly, N-(t-butoxycarbonyl)hydroxylamine is dissolved in a solvent such as THF and treated with sodium hydride. When bubbling ceases, diethyl (trifluoromethyl-

sulfonyloxymethyl)phosphonate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the N-Boc protected diethyl (aminooxymethyl)phosphonate is isolated by chromatography. The N-Boc protecting group is then removed by treatment of trifluoroacetic acid, affording the desired diethyl (aminooxymethyl)phosphonate.

Example 65 Synthesis of Representative Compounds of the Invention



10

A phosphonate pyrazole analog of prednisolone can be prepared as illustrated above. Prednisolone is reduced to 1,2-dihydroprednisolone using a rhodium catalysis such as tris(triphenylphosphine)rhodium(I) chloride under hydrogen according to a procedure such as that reported by Procopiou, P. et al, *J. Med. Chem.* 2001, 44, 602-612. The dihydroxy ketone group on the D ring of the steroid is then protected using the method described in Example 64, before formylation at the C-2 position. For example, the bis-(methylenedioxy) intermediate is treated with freshly distilled ethyl formate and sodium hydride in a solvent such as toluene. The reaction is quenched with aqueous solution of a weak base such as potassium dihydrogen phosphate. The crude product is purified by a general method such as crystallization, affording the 2-formyl

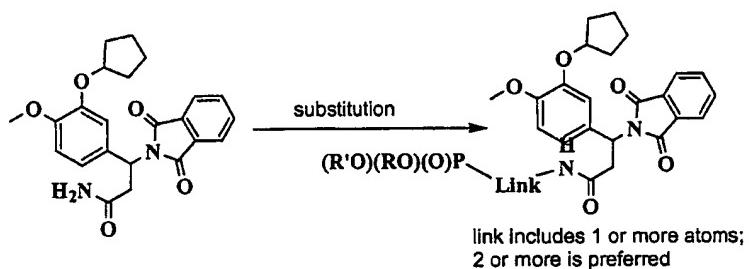
15

weak base such as potassium dihydrogen phosphate. The crude product is purified by a general method such as crystallization, affording the 2-formyl

20

intermediate. This 2-formyl compound is condensed with a phosphonate-substituted phenylhydrazine to yield, after removal of the bis-(methylenedioxy) protecting group, the desired phosphonate pyrazole analog of prednisolone. A key precursor, 3-[(diethylphosphono)methoxy]phenylhydrazine, can be made starting from diethyl (trifluoromethylsulfonyloxymethyl)phosphonate and 3-nitrophenol. 3-Nitrophenol is treated with a base such as sodium hydroxide and then *O*-alkylated with diethyl (trifluoromethylsulfonyloxymethyl)phosphonate. The nitro group is reduced with tin(II) chloride and subsequently converted to the aryl hydrazine by diazotization and reduction with sodium sulfite (*Chem. Ber.*, 1960, 93, 540) or tin(II) chloride (*J. Med. Chem.*, 2001, 44, 4031).

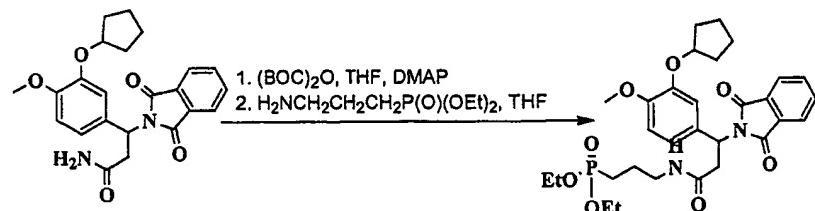
Example 66 Synthesis of Representative Compounds of the Invention



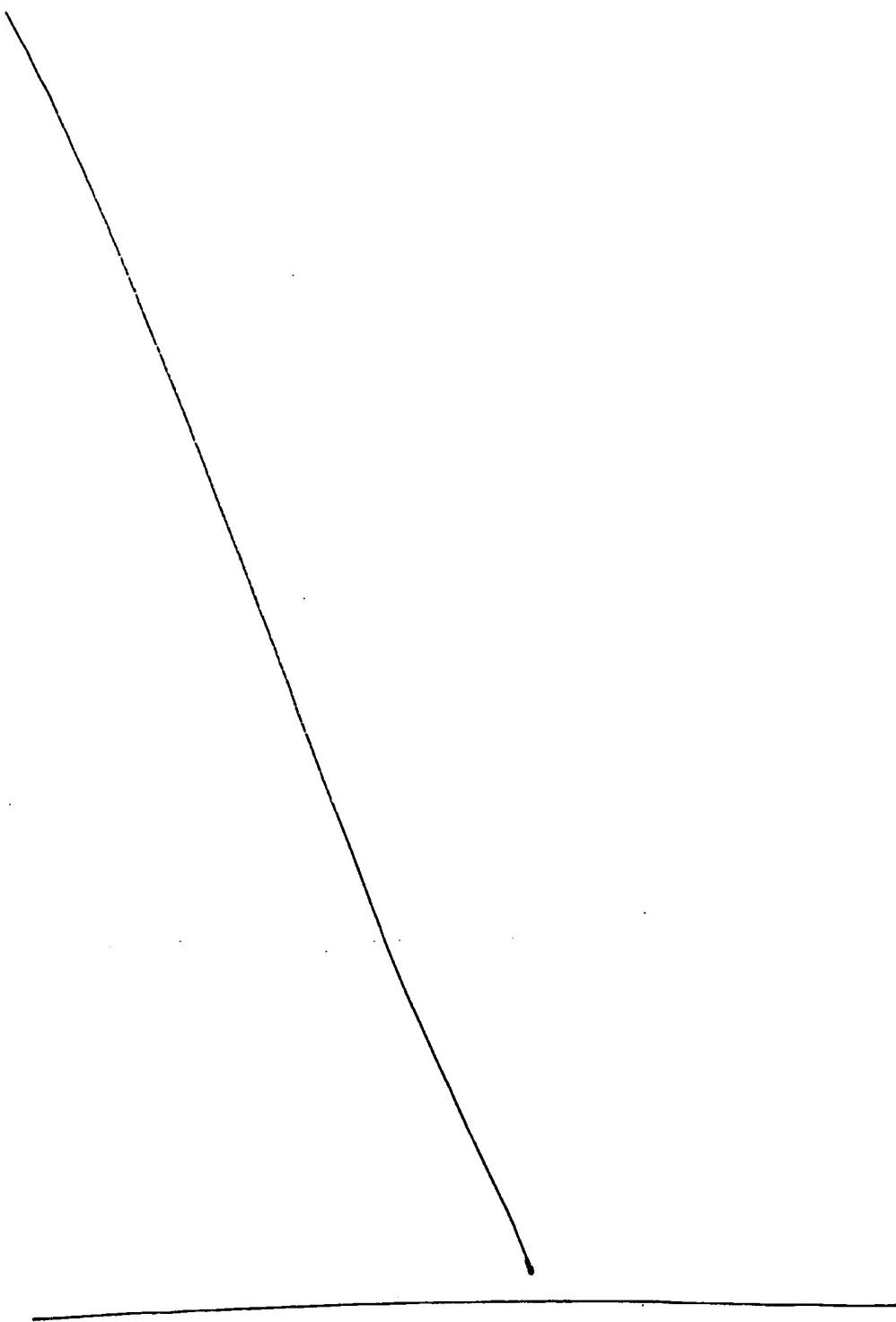
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Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

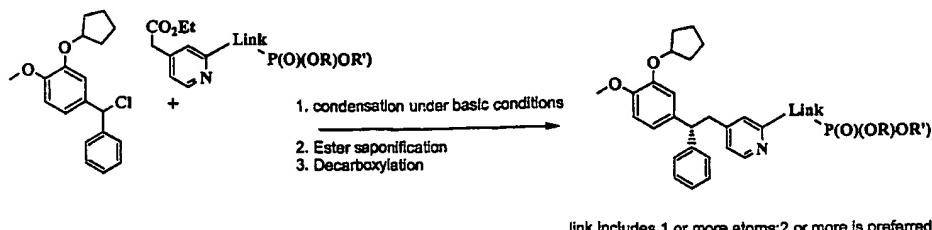
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The primary amide in CC-1088 can be acylated with $(BOC)_2O$ using N,N-dimethylaminopyridine as a base in a solvent such as tetrahydrofuran. Subsequent condensation with 3-aminopropylphosphonic acid diethyl ester in a solvent such as tetrahydrofuran gives the desired compound.



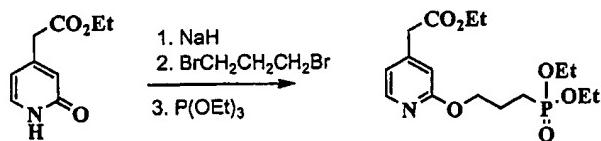
Example 67 Synthesis of Representative Compounds of the Invention



5 Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

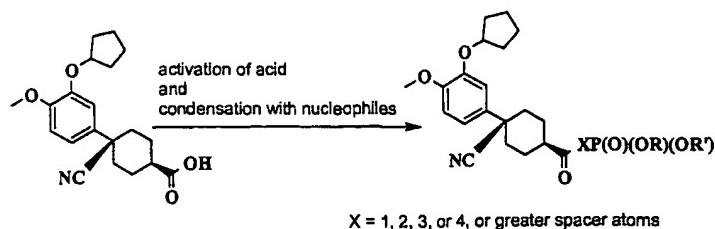
The chloride is made from (3-cyclopentyloxy-4-methoxyphenyl)phenylketone (US 5,622,977) by reduction with sodium borohydride in ethanol and treatment of the resulting alcohol with triphenylphosphine, carbon tetrachloride and diisopropyl azodicarboxylate in a solvent such as tetrahydrofuran. The condensation is achieved by treatment of the two reagents with sodium ethoxide in ethanol. The ethyl ester in the product is saponified by treatment with lithium hydroxide in ethanol, and the resulting acid is decarboxylated by heating under acidic conditions. The two enantiomers of the product may be separated by chromatography.

The synthesis of a pyridine intermediate is illustrated below.



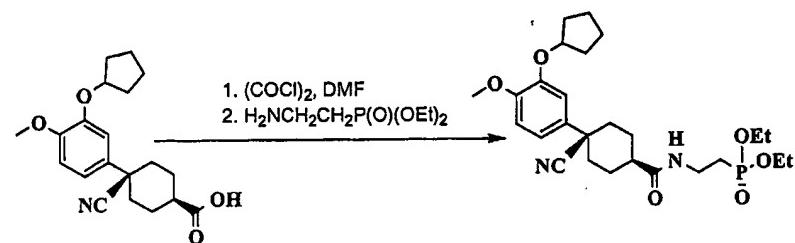
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(2-Oxo-1,2-dihydro-pyridin-4-yl)-acetic acid ethyl ester is treated with a base such as sodium hydride in a solvent such as tetrahydrofuran. After bubbling ceases, an excess of 1,3-dibromopropane is added. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-bromide is isolated by chromatography. The bromide is then heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the desired phosphonic acid.

Example 68 Synthesis of Representative Compounds of the Invention

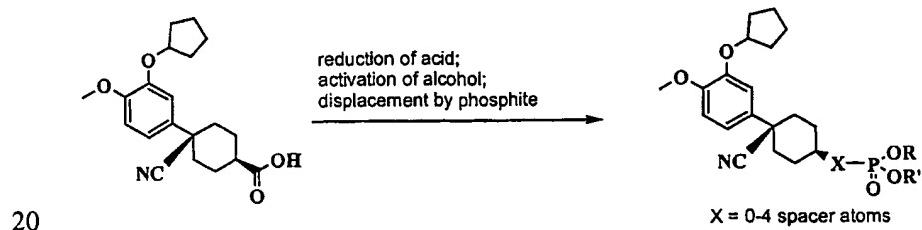
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Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.



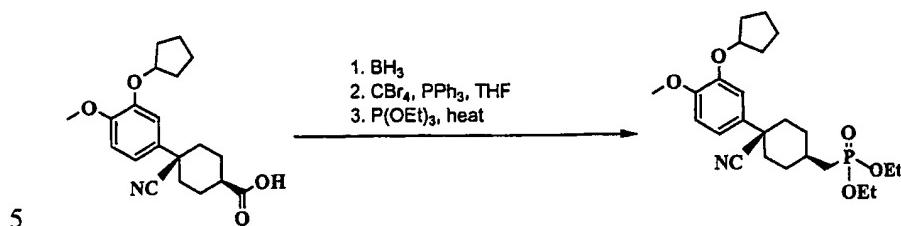
10

Cilomilast can be converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired compound.

Example 69 Synthesis of Representative Compounds of the Invention

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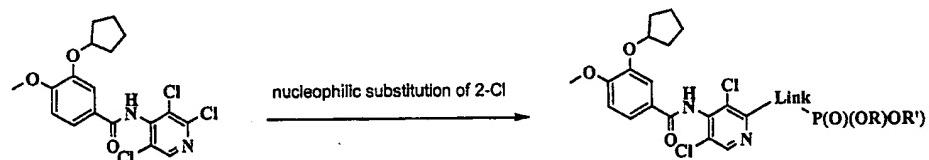
Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.



- The carboxylic acid of cilomilast can be reduced to the alcohol by treatment with diborane in a solvent such as tetrahydrofuran. The alcohol is converted to the bromide by treatment with carbon tetrabromide and triphenylphosphine in a solvent such as tetrahydrofuran or dichloromethane. The bromide is then heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the phosphonic acid.
- 10

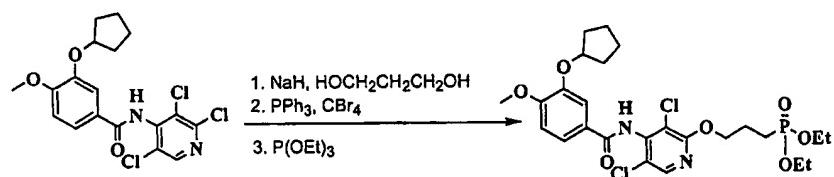
Example 70 Synthesis of Representative Compounds of the Invention

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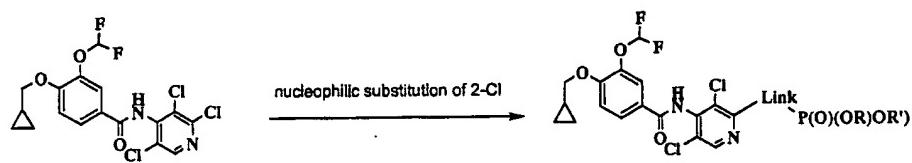
Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

20



1,3-Dihydroxypropane is treated with a base such as sodium hydride in a solvent such as tetrahydrofuran. After bubbling ceases, the 2,3,5-trichloropyridyl analog of pioclamilast (made by methods analogous to those described in US 5,698,711) is added. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated alcohol is isolated by chromatography. The alcohol is converted to the bromide by treatment with carbon tetrabromide, triphenylphosphine and diisopropyl azodicarboxylate in a solvent such as tetrahydrofuran or dichloromethane. The bromide is then heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the phosphonic acid.

Example 71 Synthesis of Representative Compounds of the Invention

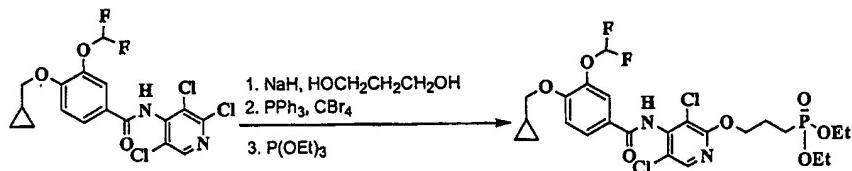


15

link includes 1 or more atoms; 2 or more is preferred

Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

20



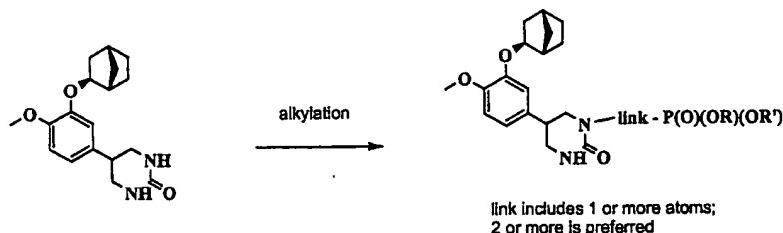
1,3-Dihydroxypropane is treated with a base such as sodium hydride in a solvent such as tetrahydrofuran. After bubbling ceases, the 2,3,5-trichloropyridyl analog of roflumilast (made by methods analogous to those described in US 5,712,298) is added. After quenching the reaction with

aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated alcohol is isolated by chromatography. The alcohol is converted to the bromide by treatment with carbon tetrabromide, triphenylphosphine and diisopropyl azodicarboxylate in a solvent such as tetrahydrofuran or dichloromethane. The bromide is then heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the phosphonic acid.

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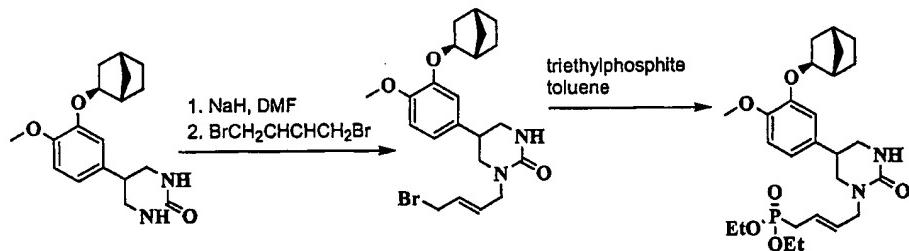
Example 72 Synthesis of Representative Compounds of the Invention

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Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

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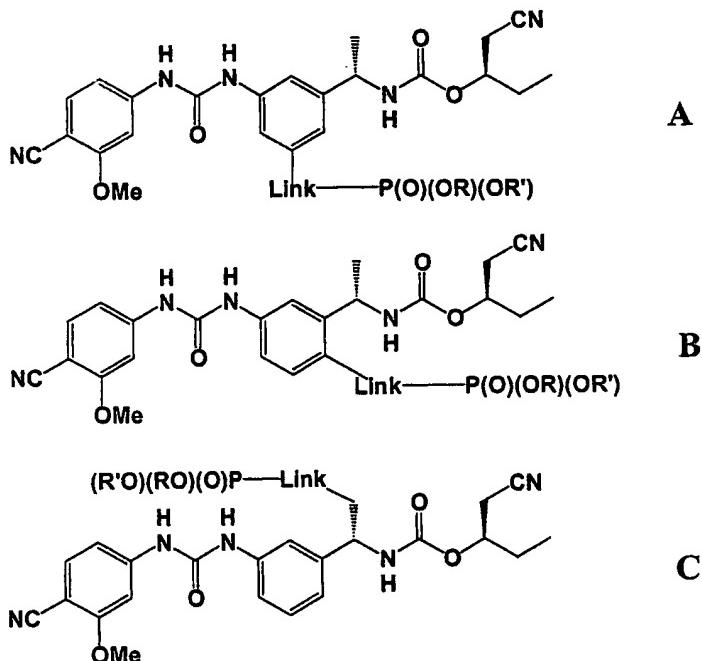


Atizoram can be treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography.

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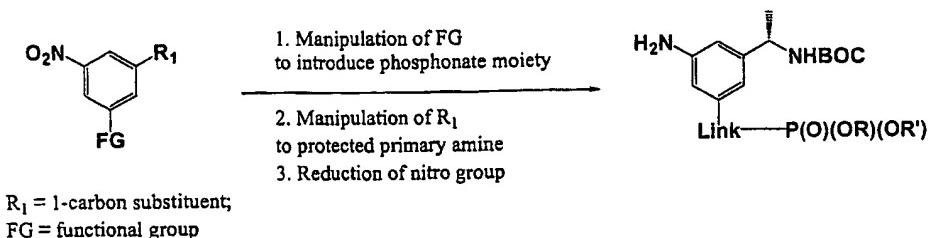
The allylic bromide is then heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the phosphonic acid.

- Synthetic methodologies and intermediate compounds that can be used to prepare VX-148 analogs of formulae A, B, or C are described in Examples 73-78. These compounds are representative examples of compounds of the invention.



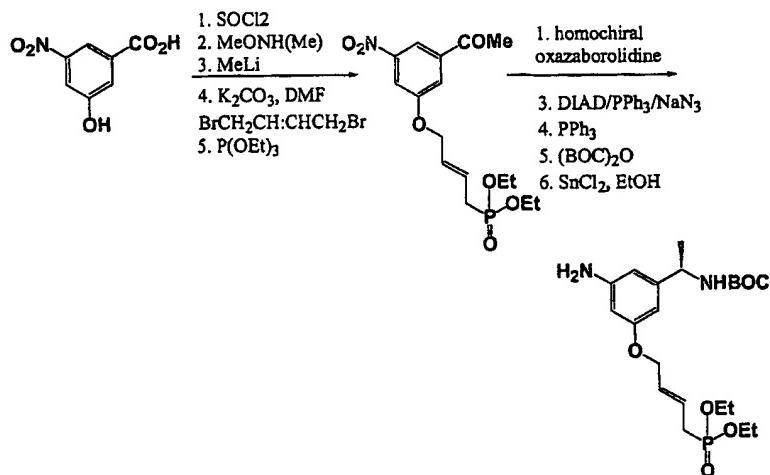
Link includes 0-8 atoms; 2 - 6 is preferred

10 Example 73 General Synthesis of Aniline Intermediates Useful for Preparing VX-148 Analogs of the Invention.



A general scheme that is useful for converting a 3,5-difunctionalized nitrobenzene derivative to an aniline that can be used to prepare a VX-148 analog of the invention is illustrated above.

5 Example 74 Synthesis of Aniline Intermediates Useful for Preparing VX-148 Analogs of the Invention.

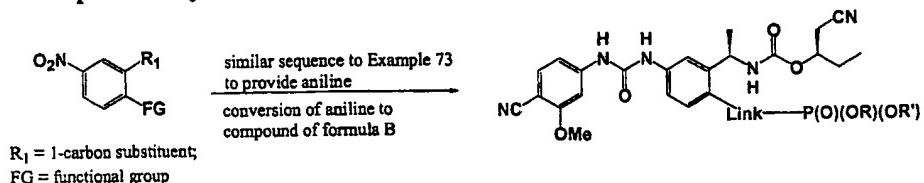


- 3-Hydroxy-5-nitro-benzoic acid is heated briefly in thionyl chloride to generate the acid chloride. This is then condensed with O,N -dimethylhydroxylamine in the presence of a base such as triethylamine to produce the Weinreb amide which, upon reaction with methyl lithium, gives the acetophenone derivative. This is then treated with a base such as potassium carbonate in a dipolar aprotic solvent such as dimethyl-formamide, in the presence of an excess of *E*-1,4-dibromobutene. The monobromide is isolated by chromatography and then subjected to treatment with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) to generate the desired phosphonate diethyl ester. Thereafter, the carbonyl of the acetophenone is reduced enantioselectively using an appropriate homochiral oxazaborolidine such as that described by Corey (*J. Am. Chem. Soc.*, 1987, 109, 5551), and the resulting alcohol is displaced by azide using a method such as that described by Mitsunobu (*Bull. Chem. Soc. Japan.*, 1971, 44, 3427). The azide is reduced to

the amine under Staudinger conditions (*Helv. Chim. Act.*, 1919, 2, 635) and protected as the t-butyl carbamate. Finally, the desired aniline intermediate is generated by tin (II)-mediated reduction of the nitrobenzene.

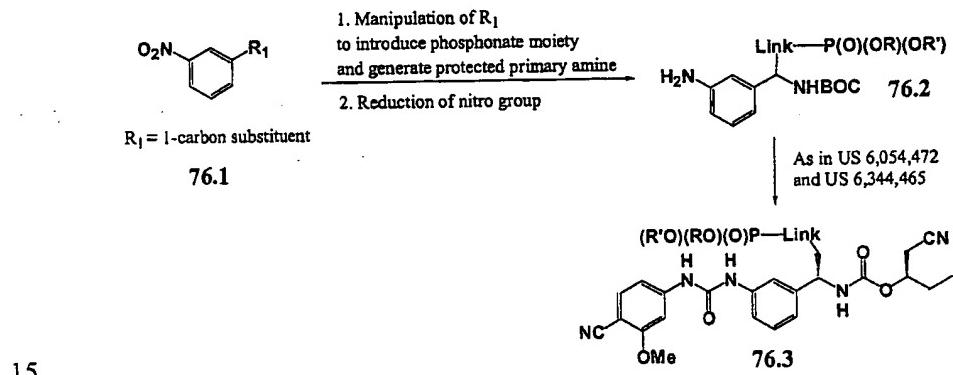
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Example 75 Synthesis of VX-148 Analogs of the Invention.



A general scheme that is useful for converting a 3,4-difunctionalized nitrobenzene derivative to an aniline, which can be converted to a compound of formula B using coupling reactions similar to those described in US 6,054,472 and US 6,344,465, is illustrated above.

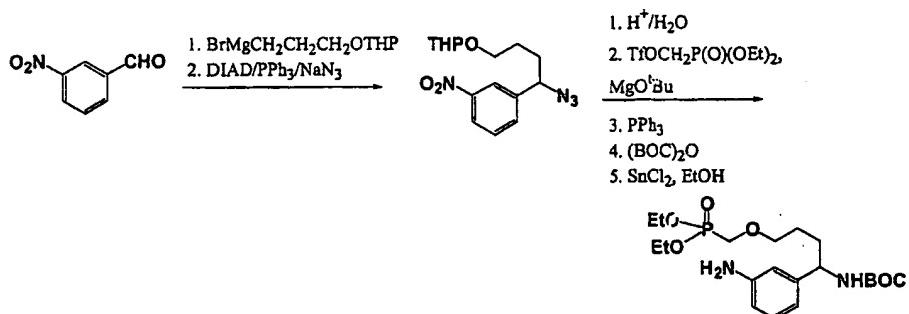
Example 76 General Route to Representative Compounds of the Invention



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Manipulation of a 3-substituted nitrobenzene 76.1 provides aniline 76.2, which can be converted to a compound of formula C using coupling reactions similar to those described in US 6,054,472 and US 6,344,465.

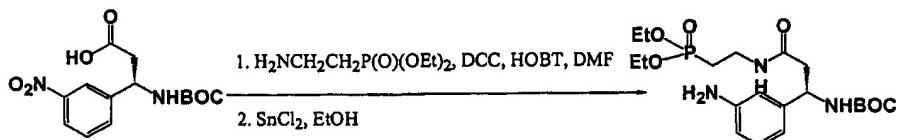
Example 77 General Route to Aniline Intermediates Useful For Preparing Representative Compounds of the Invention



5 3-Nitrobenzaldehyde reacts with a Grignard reagent to introduce a tether bearing a protected alcohol and simultaneously to generate a benzylic alcohol, as shown. The alcohol is displaced by an azide in a manner similar to that described for Example 9. After deprotection, the liberated alcohol is alkylated with diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) using a base such as magnesium tert-butoxide in a solvent such as tetrahydrofuran. Subsequent transformations of the azide and nitro groups proceed in a fashion similar to that described in Example 74. See Batt et al, *Bioorg. Med. Chem. Lett.*, 1995, 5, 1549.

10

15 **Example 78 General Route to Aniline Intermediate Useful For Preparing Representative Compounds of the Invention**

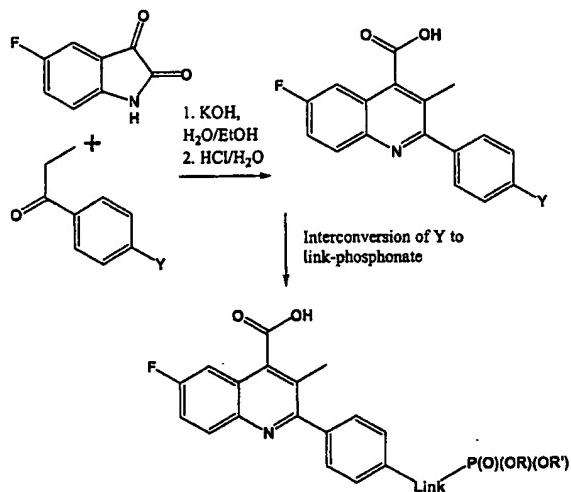


20 *3-tert-Butoxycarbonylamino-3-(3-nitro-phenyl)-propionic acid* (commercially available) is coupled with 2-aminoethylphosphonic acid diethyl ester (commercially available) using standard reagents for the formation of a secondary amide such as dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBT), in a solvent such as dimethylformamide.

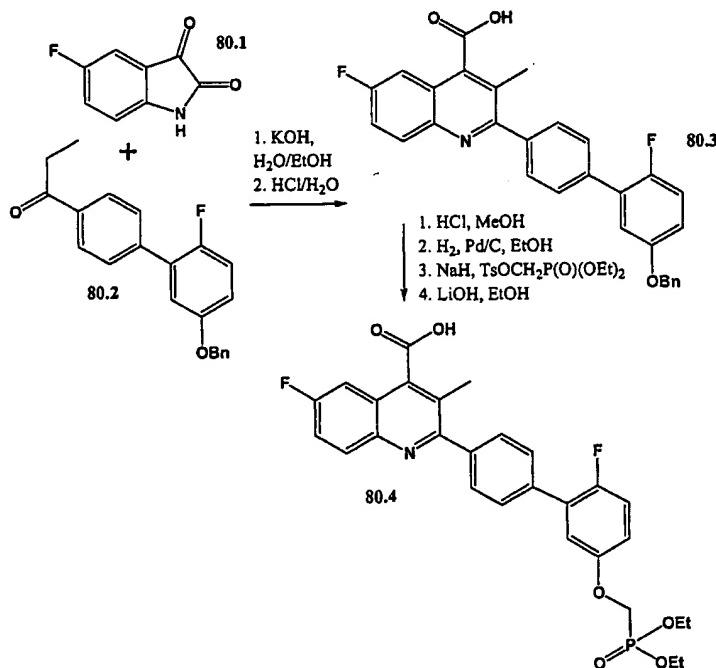
Subsequent reduction of the nitro group proceeds in a fashion similar to that described in Example 74.

Example 79 General Route to Representative Compounds of the Invention

The following is a general route that can be used to prepare compounds 5 of the invention.

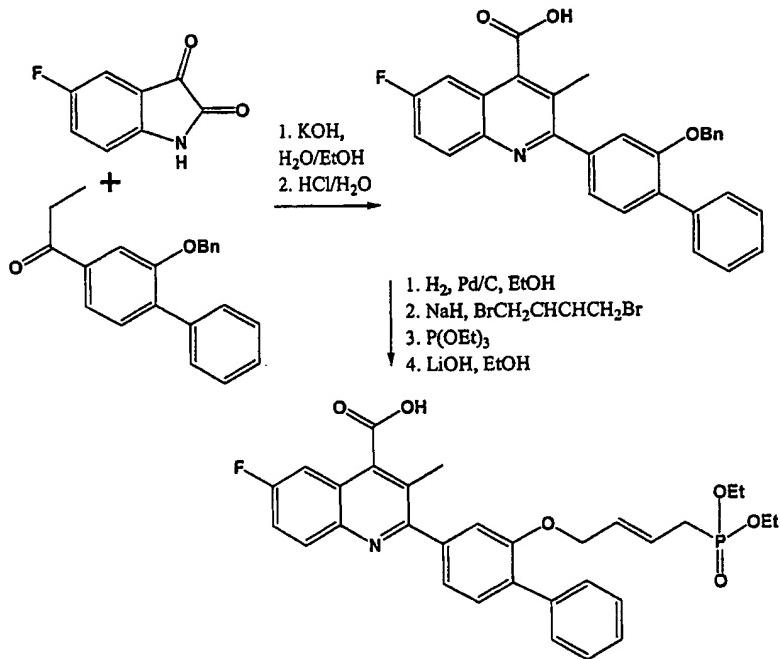


Example 80 Preparation of a Representative Compound of the Invention



The initial Pfitzinger condensation of compound 80.1 and compound 80.2 is achieved in a single step using potassium hydroxide with acidic work-up, as shown. Alternatively, the initial aldol condensation may be performed using diethylamine in ethanol, and the quinoline ring may be formed as a second step mediated by an acid such as hydrochloric acid in a solvent such as 1,4-dioxane. Following removal of the benzyl protecting group via hydrogenation, the phenol can be treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl 10 phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added, yielding the desired phosphonate diester. The carboxylate is deprotected by treatment with lithium hydroxide in ethanol to provide the compound 80.4 (which is a compound of the invention).

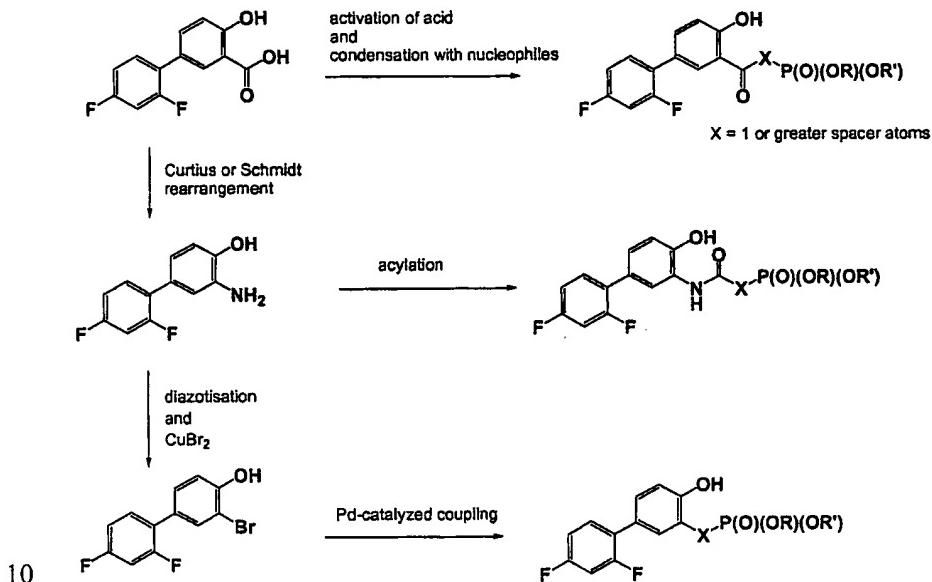
15 **Example 81 Preparation of a Representative Brequinar Phosphonate Analogs of the Invention**



The synthesis is similar to that depicted in Example 80 except that, 20 following deprotection of the phenol, *E*-1,4-dibromobutene is added in excess.

After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The resulting bromide is heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the desired phosphonic acid, and the carboxylic acid is deprotected as before to provide a compound of the invention.

Example 82 Preparation of Representative Compounds of the Invention



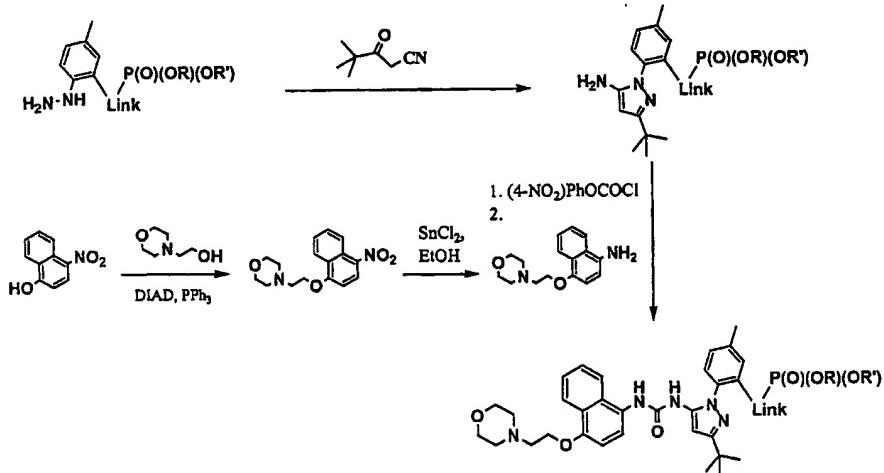
Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

- 15 Diflunisal is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product:
- 20 Diflunisal is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated

with diluted hydrochloric acid to provide the aniline (*J. Org. Chem.*, 2002, 67, 6260). The aniline is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid is obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The aniline derived from diflunisal is converted to the aryl bromide using a variant of the Sandmeyer reaction (*Bull. Chem. Soc. Jpn.*, 1980, 53, 1065). This is then coupled with pent-4-ynyl-phosphonic acid diethyl ester (generated from 5-chloro-1-pentyne and triethylphosphite in a solvent such as toluene, or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) under conditions such as those pioneered by Sonagashira (Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, 1975, 4467) to afford the desired diflunisal analog containing a phosphonate.

Example 83 Preparation of Representative Compounds of the Invention

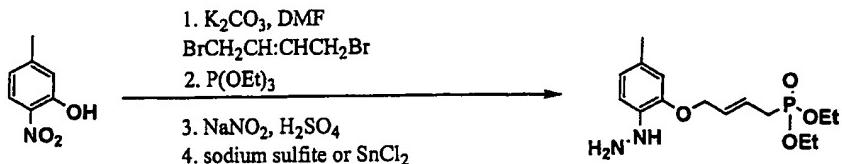


20

Representative compounds of the invention can be prepared as illustrated above. The aryl hydrazine is condensed with 4,4-dimethyl-3-oxo-pentanenitrile to form an aminopyrazole (as described in *J. Med. Chem.*, 2002, 45, 2994). Urea formation is accomplished by sequential condensation with 4-nitrophenyl

chloroformate and the requisite aniline. The latter is generated from 4-nitro-naphthalen-1-ol by reaction with 2-morpholin-4-yl-ethanol using a method such as that described by Mitsunobu (*Bull. Chem. Soc. Japan*, 1971, 44, 3427), followed by tin(II)-mediated reduction of the nitro group to provide the aniline.

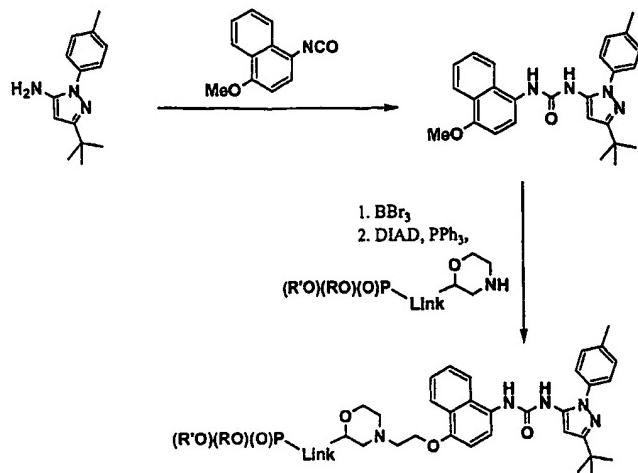
- 5 The synthesis of a suitable phosphonate-containing arylhydrazine intermediate is illustrated below.



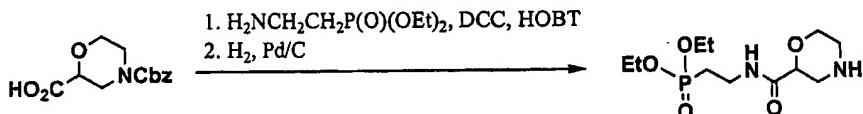
- 10 5-Methyl-2-nitrophenol is alkylated with *E*-1,4-dibromobutene. The resulting monobromide is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. The nitro group is converted to the aryl hydrazine by diazotization and reduction with sodium sulfite (*Chem. Ber.*, 1960, 93, 540) or tin(II) chloride (*J. Med. Chem.*, 2001, 44, 4031).

- 15 The syntheses of suitable phosphonate-containing aryl hydrazines in which link is attached to the 3- or 4-positions of the phenyl ring are analogous to that shown in Example 83, starting from 2-methyl-5-nitrophenol and 4-nitrophenol, respectively.

Example 84 Preparation of Representative Compounds of the Invention



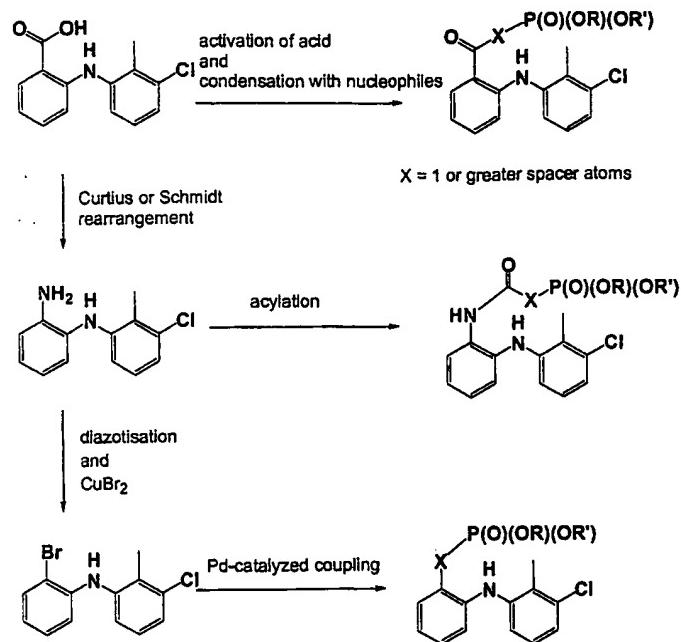
- Representative compounds of the invention can be prepared as illustrated above. Following the synthesis of the urea through condensation of 5-tert-butyl-2-p-tolyl-2H-pyrazol-3-ylamine and 1-isocyanato-4-methoxy-naphthalene, the product is demethylated by treatment with a Lewis acid such as boron tribromide. The resulting phenol is coupled with a suitable morpholine derivative using a method such as that described by Mitsunobu (*Bull. Chem. Soc. Japan.*, 1971, 44, 3427).
- The synthesis of a suitable phosphonate-containing morpholine intermediate is illustrated below.



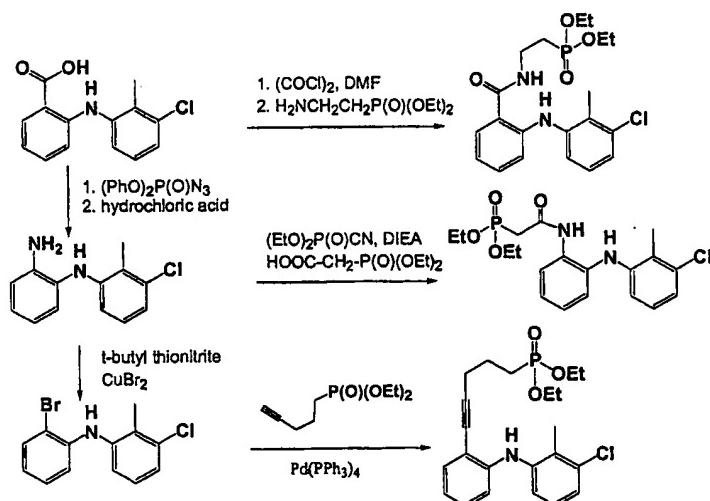
- Morpholine-2,4-dicarboxylic acid 4-benzyl ester (generated from morpholine-2,4-dicarboxylic acid by reaction with benzyl chloroformate under standard protection conditions (such as those described in Greene, T., Protective groups in organic synthesis, Wiley-interscience, 1999)) is coupled with 2-aminoethylphosphonic acid diethyl ester (commercially available) using standard reagents for the formation of a secondary amide such as dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBT), in a solvent such as dimethylformamide. Removal of the benzyl carbamate protecting group

by hydrogenation over palladium in a solvent such as methanol (as described in Greene, T. *ibid.*) provides the desired product.

Example 85 Preparation of Representative Compounds of the Invention



5 Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

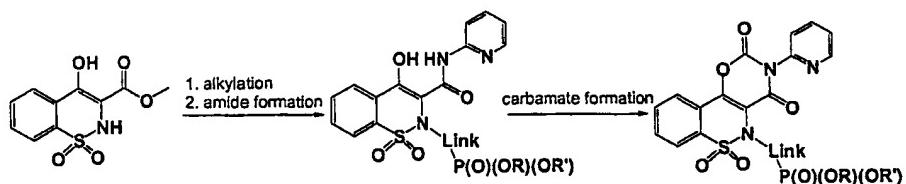


Tolfenamic acid is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

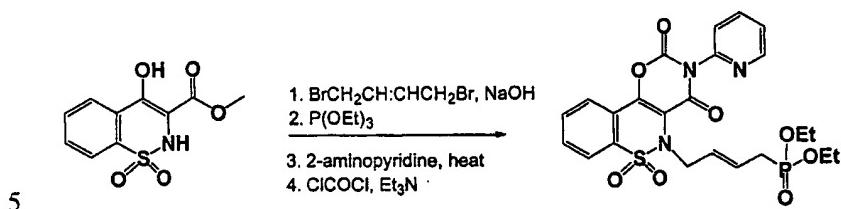
5 Tolfenamic acid is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the aniline (*J. Org. Chem.*, 2002, 67, 10 6260). The aniline is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid is obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such 15 as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The aniline derived from tolfenamic acid is converted to the aryl bromide using a variant of the Sandmeyer reaction (*Bull. Chem. Soc. Jpn.*, 1980, 53, 20 1065). This is then coupled with pent-4-ynyl-phosphonic acid diethyl ester (generated from 5-chloro-1-pentyne and triethylphosphite in a solvent such as toluene, or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) under conditions such as those pioneered by Sonagashira (Sonogashira, K.; Tohda, Y.; Hagiwara, N. *Tetrahedron Lett.*, 1975, 4467) to generate the desired phosphonate-containing 25 analog of tolfenamic acid.

Example 86 Preparation of Representative Compounds of the Invention



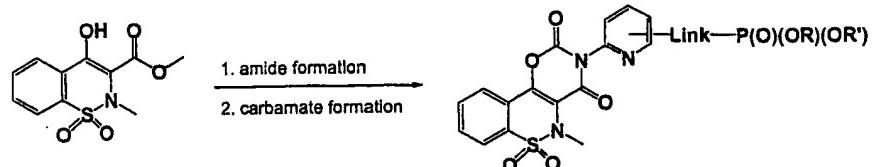
Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.



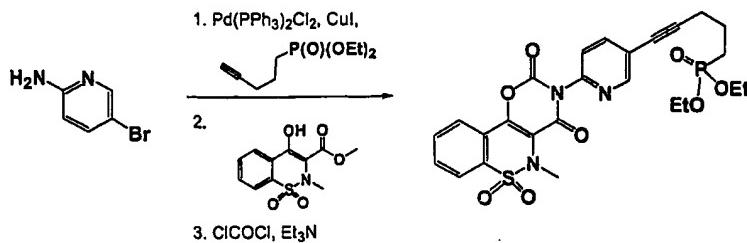
The methyl ester shown is treated in a solvent such as ethanol with excess *E*-1,4-dibromobutene in the presence of a base such as sodium hydroxide, as described in *J. Med. Chem.*, 1997, 40, 980. The monobromide so formed is 10 then heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. Heating with 2-aminopyridine in solvents such as xylenes, as described in *J. Med. Chem.*, 1997, 40, 980, gives the desired piroxicam analogue, which is 15 transformed to the corresponding droxicam-like prodrug by treatment with phosgene and a tertiary amine such as triethylamine in solvents such as tetrahydrofuran and/or benzene, as described in *J. Med. Chem.*, 1973, 16, 44.

Example 87 Preparation of Representative Compounds of the Invention

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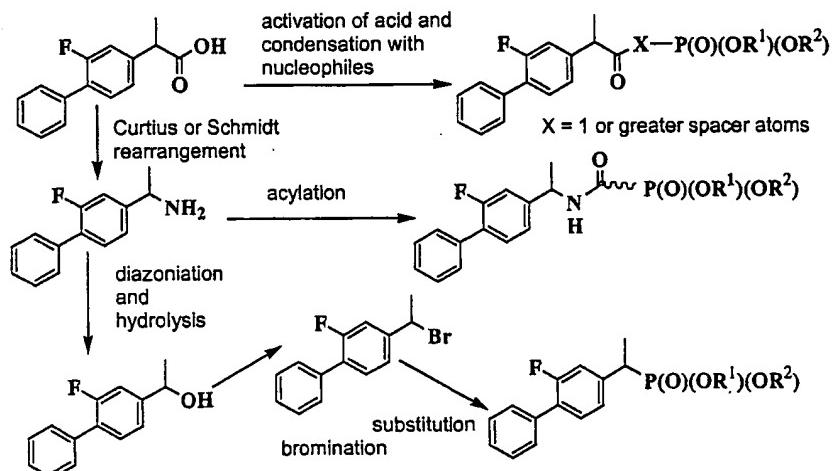
Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as 25 follows.



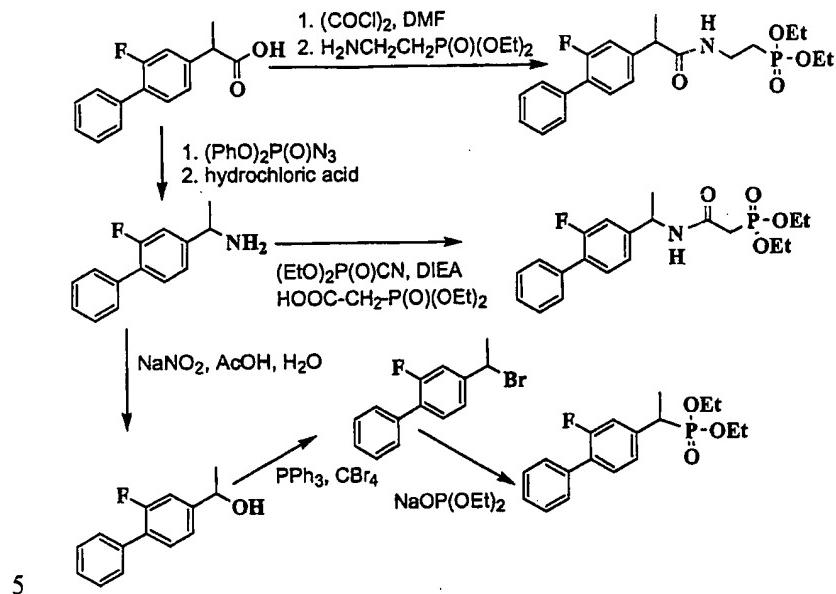
2-Amino-5-bromopyridine is coupled with pent-4-ynyl-phosphonic acid diethyl ester (generated from 5-chloro-1-pentyne and triethylphosphite in a solvent such as toluene, or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press, 1988) under conditions such as those pioneered by Sonagashira (Sonogashira, K.; Tohda, Y.; Hagiwara, N. *Tetrahedron Lett.*, 1975, 4467) to afford the desired phosphonate-containing aminopyridine. This is then heated with the methyl ester shown in solvents such as xylenes, as described in *J. Med. Chem.*, 1997, 40, 980, to give the desired piroxicam analogue, which is transformed to the corresponding droxicam-like prodrug by treatment with phosgene and a tertiary amine such as triethylamine in solvents such as tetrahydrofuran and/or benzene, as described in *J. Med. Chem.*, 1973, 16, 44.

15

Example 88 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.



Flurbiprofen is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

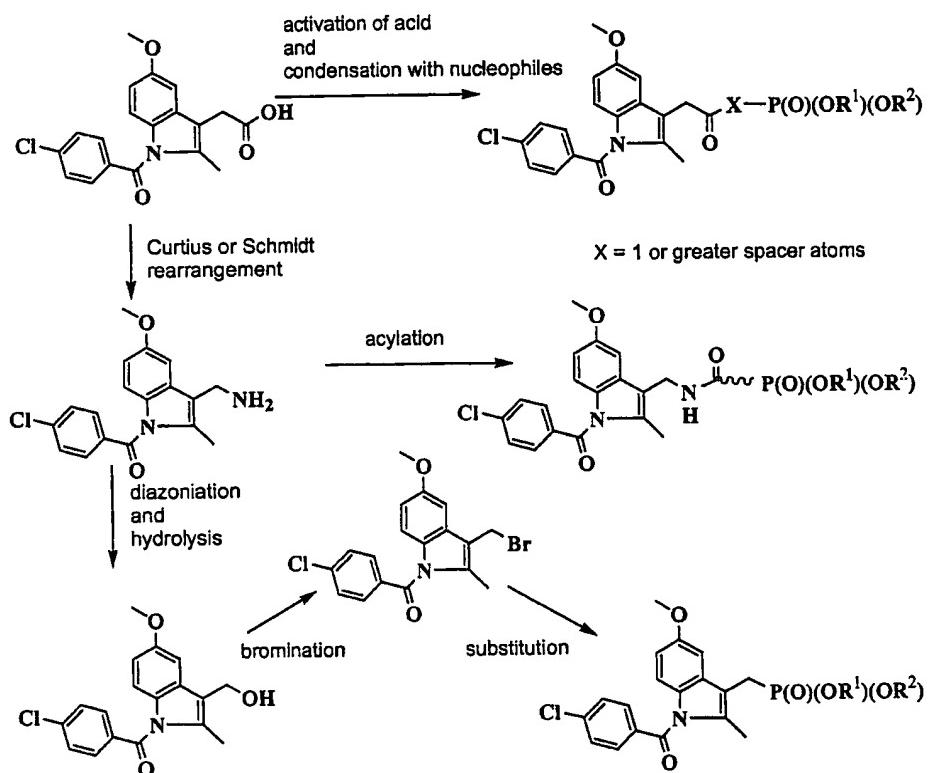
Flurbiprofen is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid is obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The amine derived from flurbiprofen can be converted to the alcohol, according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159.

Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol.

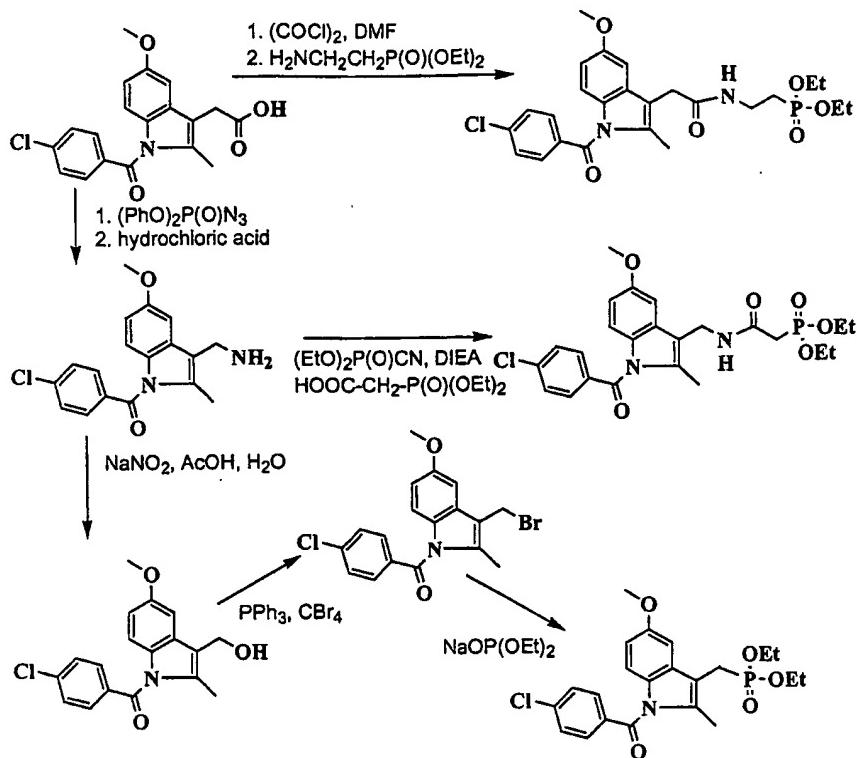
- 5 The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of flurbiprofen, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.
- 10

Example 89 Preparation of Representative Compounds of the Invention



15

Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.



Indomethacin is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

Indomethacin is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The amine derived from indomethacin can be converted to the alcohol, according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159.

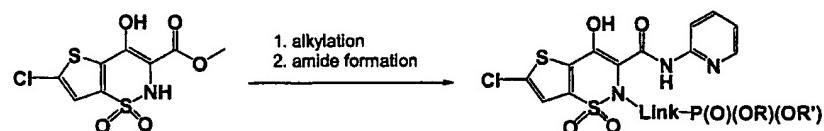
Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol.

- 5 The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of indomethacin, according to a
- 10 procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

Example 90 Preparation of Representative Compounds of the Invention

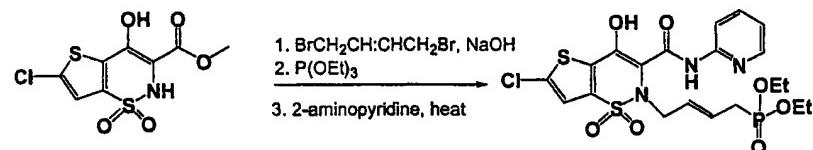
Compounds of the invention can be prepared as generally described in Schemes 1 and 2, with examples depicted in Examples 1 and 2.

15



Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

20

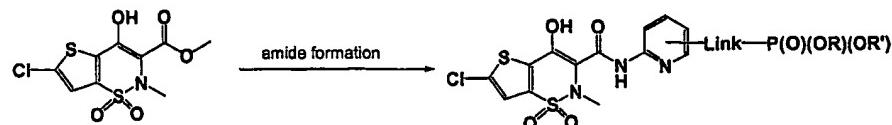


- 25 The methyl ester shown (made from the des-chloro compound (*J. Med. Chem.*, 1987, 30, 678) by treatment with N-chlorosuccinimide in a solvent such as dichloromethane) is treated in a solvent such as ethanol with excess *E*-1,4-dibromobutene in the presence of a base such as sodium hydroxide, as described in *J. Med. Chem.*, 1997, 40, 980. The monobromide so formed is then heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction

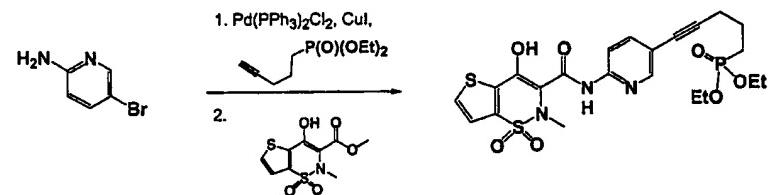
conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. Finally, heating with 2-aminopyridine in solvents such as xylenes, as described in *J. Med. Chem.*, 1997, 40, 980, gives the desired analogue.

5

Example 91 Preparation of Representative Compounds of the Invention



10 Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

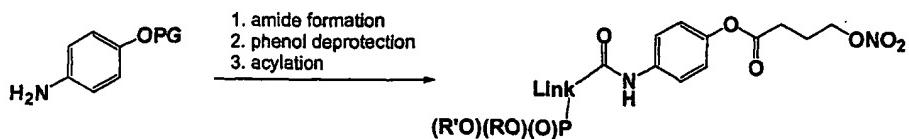


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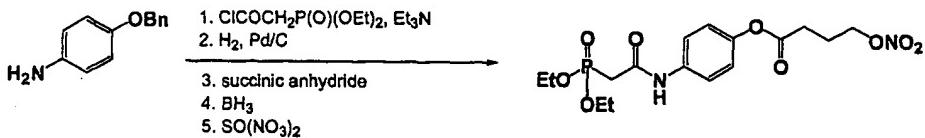
2-Amino-5-bromopyridine is coupled with pent-4-ynyl-phosphonic acid diethyl ester (generated from 5-chloro-1-pentyne and triethylphosphite in a solvent such as toluene, or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) under conditions such as those pioneered by Sonagashira (Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, 1975, 4467) to afford the desired phosphonate-containing aminopyridine. This is then heated with the methyl ester shown in solvents such as xylenes, as described in *J. Med. Chem.*, 1997, 40, 980, to give the desired lornoxicam analogue.

20

Example 92 Preparation of Representative Compounds of the Invention



5 Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.



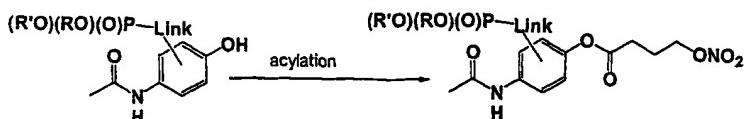
10

4-Benzylxylaniline is condensed with diethyl phosphonoacetic acid chloride (formed from diethyl phosphonoacetic acid by treatment with oxalyl chloride, in the presence of a catalytic amount of dimethylformamide, in a solvent such as dichloromethane) in the presence of a base such as triethylamine.

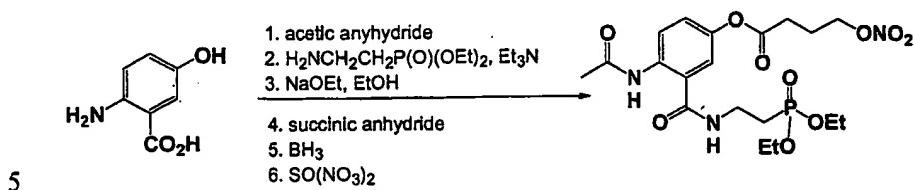
15 The phenol is liberated by hydrogenation over a catalyst of palladium on charcoal according to Greene, Protective Groups in Synthesis, Wiley, 1999. This is then condensed with succinic anhydride using a base such as sodium hydride in a solvent such as tetrahydrofuran (*Bioorg. Med. Chem. Lett.*, 2002, 12, 2545). The acid so formed is reduced with diborane in a solvent such as 20 tetrahydrofuran, and the resulting primary alcohol is reacted with the nitrating reagent shown in a solvent such as tetrahydrofuran (*Helv. Chim. Act.*, 1984, 67, 906).

Example 93 Preparation of Representative Compounds of the Invention

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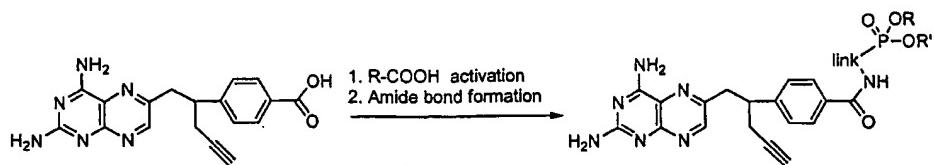


Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

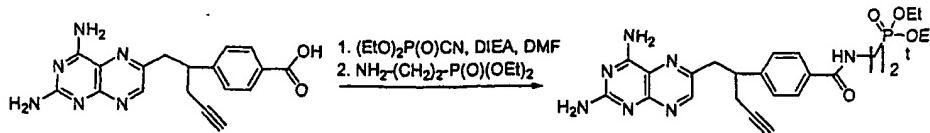


- 5-Hydroxyanthranilic acid is heated with acetic anhydride, generating the tri-acetylated species. This is then allowed to react with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the phosphonate-containing amide. Following deprotection of the phenol by treatment with sodium ethoxide, the nitrate-containing side-chain is constructed by initial condensation with succinic anhydride using a base such as sodium hydride in a solvent such as tetrahydrofuran (*Bioorg. Med. Chem. Lett.*, 2002, 12, 2545), reduction of the acid so formed with diborane in a solvent such as tetrahydrofuran, and finally reaction of the resulting primary alcohol with the nitrating reagent shown in a solvent such as tetrahydrofuran (*Helv. Chim. Act.*, 1984, 67, 906).

20 **Example 94 Preparation of Representative Compounds of the Invention**



- Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

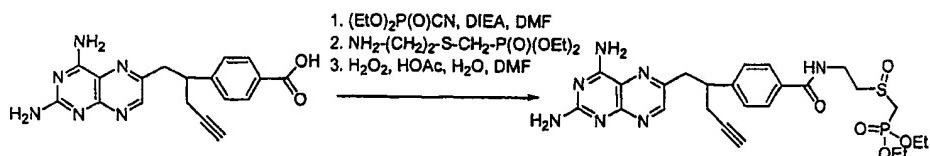


The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl

- 5 chloroformate and a base such as diisopropylethylamine (DIEA) at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation is complete, 2-aminoethylphosphonic acid diethyl ester (commercially available) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the product is isolated
- 10 via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like.

Example 95 Preparation of Representative Compound of the Invention

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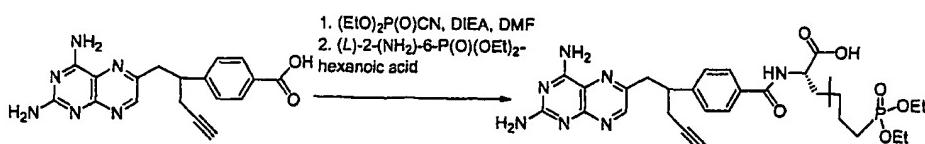


The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl

- 20 chloroformate and a base such as diisopropylethylamine (DIEA) at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604). When the activation is complete, (2-amino-ethylsulfanyl methyl)-phosphonic acid diethyl ester (made by base-catalyzed coupling of 2-aminoethanethiol with diethyl phosphonomethyltriflate, prepared according to
- 25 *Tetrahedron Lett.*, 1986, 27, 1477) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the intermediate is isolated via chromatography. Alternatively, the intermediate can be isolated through precipitation from the reaction solution with an organic solvent like

diethyl ether or the like. The intermediate is then dissolved in a mixture of water, DMF, and acetic acid and is treated with hydrogen peroxide solution (excess). After removal of the solvents the product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like.

Example 96 Preparation of Representative Compounds of the Invention



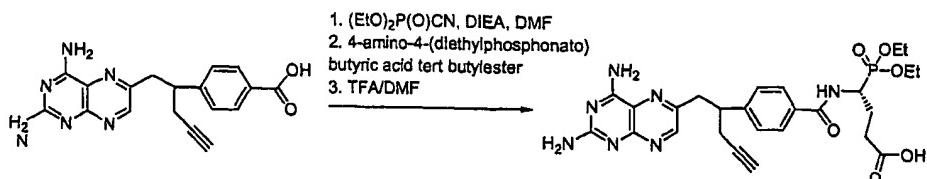
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The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as DIEA at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604.). When the activation is complete, (*L*)-2-amino-6-(diethylphosphonato)-hexanoic acid is added. After consumption of the activated species is observed the solvent is removed in vacuo and the product is isolated via chromatography. Alternatively, the product can be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like.

15

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Example 97 Preparation of Representative Compounds of the Invention

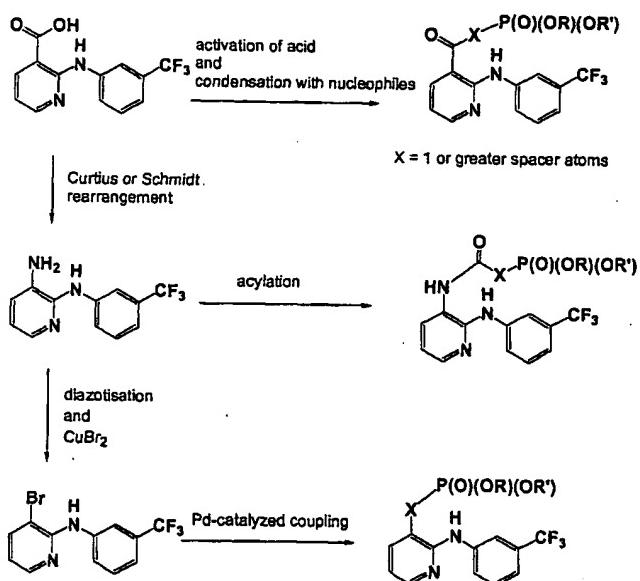


25

The starting carboxylic acid can be treated in a solvent such as DMF or NMP with a coupling reagent such as diethyl cyanophosphonate or isobutyl chloroformate and a base such as DIEA at room temperature (*J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604.). When the activation

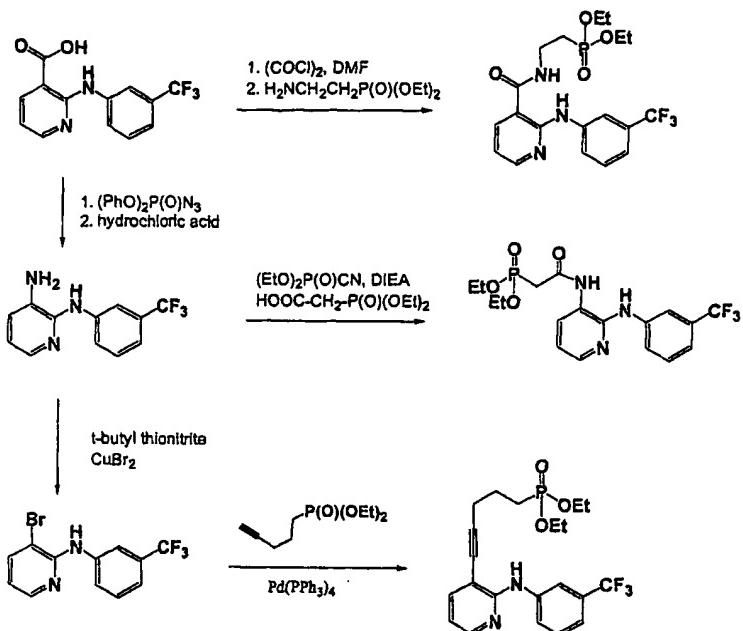
is complete, 4-amino-4-(diethylphosphonato)-butyric acid tert butylester (*J. Am. Chem. Soc.*, 1995, 117, 10879-10888) is added. After consumption of the activated species is observed the solvent is removed in vacuo and the intermediate is isolated via chromatography. Alternatively, the intermediate can
 5 be isolated through precipitation from the reaction solution with an organic solvent like diethyl ether or the like. The crude intermediate is then dissolved in DMF and treated with TFA (excess). The product is isolated via chromatography after removal of the solvents. Alternatively, the product can be isolated through precipitation form the reaction solution with an organic solvent like diethyl ether
 10 or the like

Example 98 Preparation of Representative Compounds of the Invention



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Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.



- Niflumic acid is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.
- 5 Niflumic acid is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room

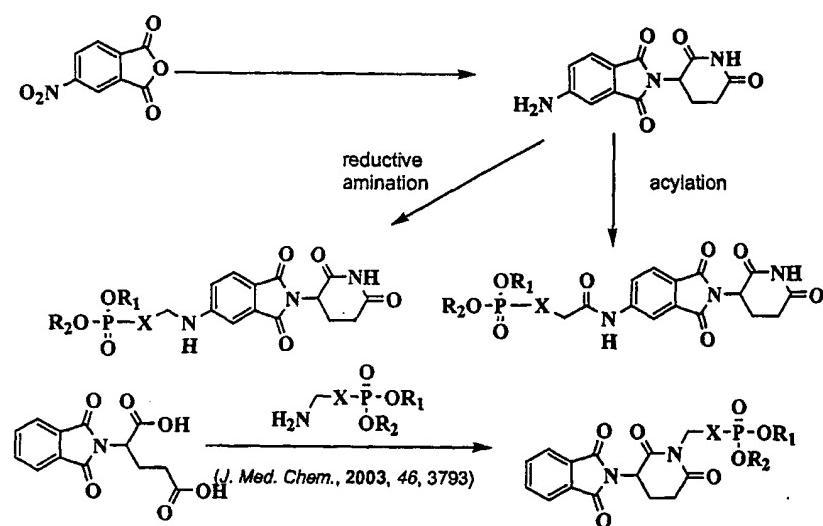
10 temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the aniline (*J. Org. Chem.*, 2002, 67, 6260). The aniline is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 15 1984, 27, 600-604. The activated diethylphosphonoacetic acid is obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The aniline derived from niflumic acid is converted to the aryl bromide 20 using a variant of the Sandmeyer reaction (*Bull. Chem. Soc. Jpn.*, 1980, 53, 1065). This is then coupled with pent-4-ynyl-phosphonic acid diethyl ester

(generated from 5-chloro-1-pentyne and triethylphosphite in a solvent such as toluene, or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) under conditions such as those pioneered by Sonagashira (Sonogashira, K.; Tohda, Y.; Hagihara, N.

- 5 *Tetrahedron Lett.*, 1975, 4467) to generate the desired phosphonate-containing analog of niflumic acid.

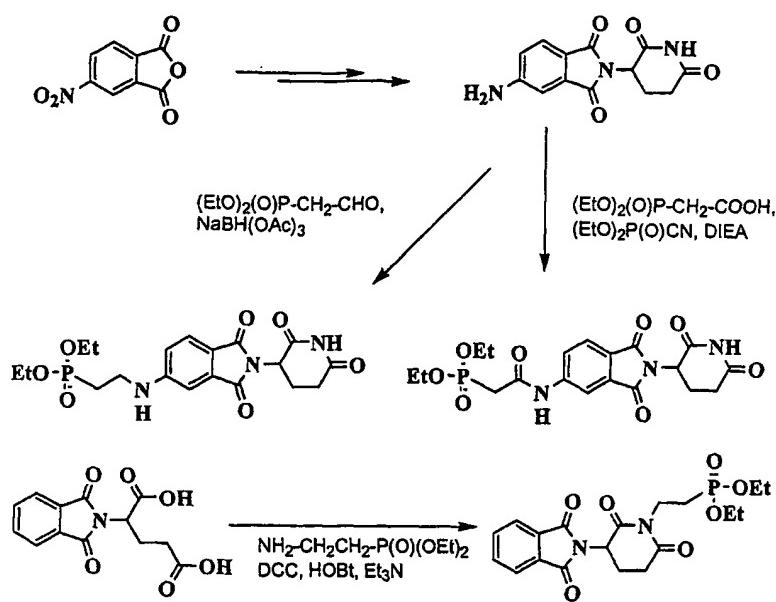
Example 99 Preparation of Representative Compounds of the Invention



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 $\text{X} = 0 \text{ to } 4 \text{ atoms spacer}$

Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.



5-Nitro-isobenzofuran-1,3-dione (commercially available) is converted to 5-amino-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione following the

5 procedures reported in *Bioorg. Med. Chem. Lett.*, 1999, 9, 1625. This amine intermediate is subjected to a reductive amination with diethylphosphonoacetaldehyde (obtained from ozonolysis of diethyl allylphosphonate) in the presence of a reducing agent such as sodium triacetoxyborohydride to generate the desired amine linker analog (*J. Org. Chem.*, 1996, 61, 3849). Alternatively, the amine is acylated with an activated

10 diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960 and *J. Med. Chem.*, 1984, 27, 600. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a

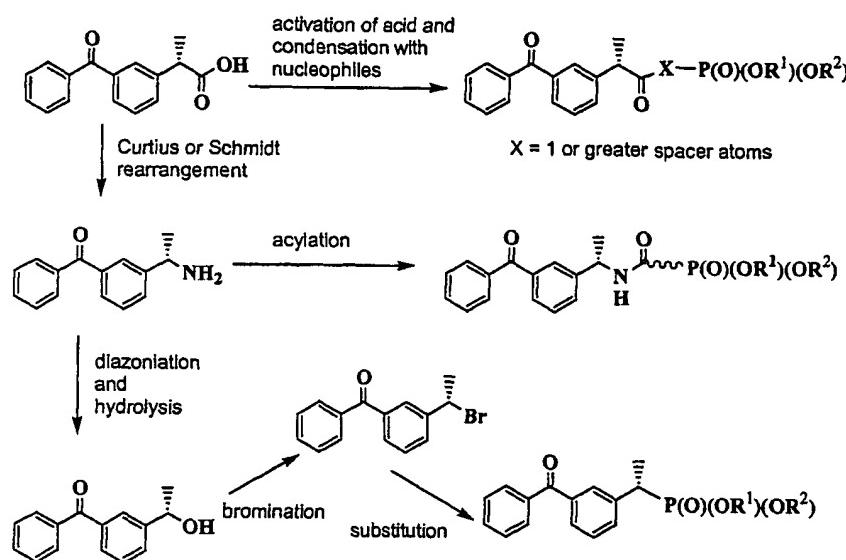
15 coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentanedioic acid (commercially available) is treated in a solvent such as acetonitrile with triethylamine, 1-hydroxybenzotriazole, 4-methoxybenzylamine, and 1,3-20 dicyclohexylcarbodiimide. After the reaction is complete, the solvent is removed and the residue is purified by chromatography to generate the desired

analog, according to a procedure such as that reported in *J. Med. Chem.*, 2003, 46, 3793.

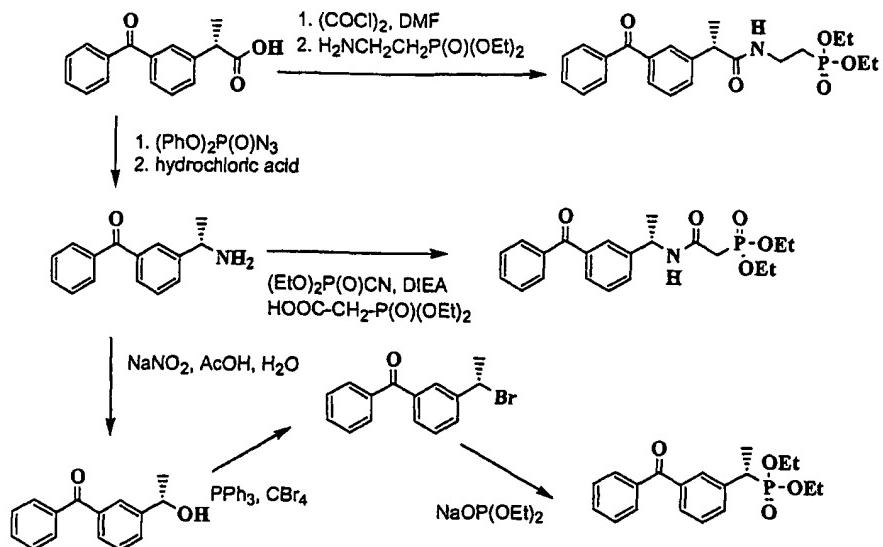
Example 100 Preparation of Representative Compounds of the Invention

5



Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

10



Dexketoprofen is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-

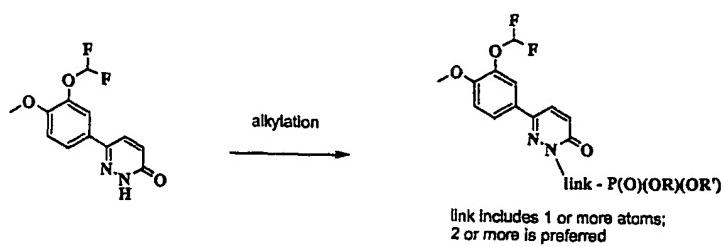
- 5 aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

Dexketoprofen is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room 10 temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 15 1984, 27, 600-604. The activated diethylphosphonoacetic acid is obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

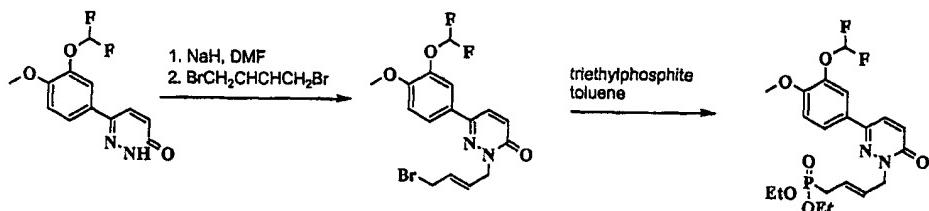
The amine derived from dexketoprofen is converted to the alcohol, 20 according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159. Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol.

The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester 5 to provide the desired phosphonate derivative of dexketoprofen, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

Example 101 Preparation of Representative Compounds of the Invention

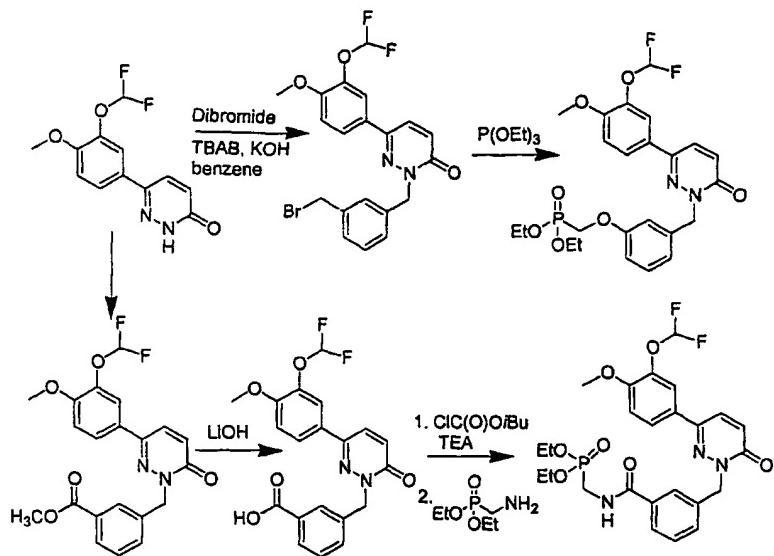


5 Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

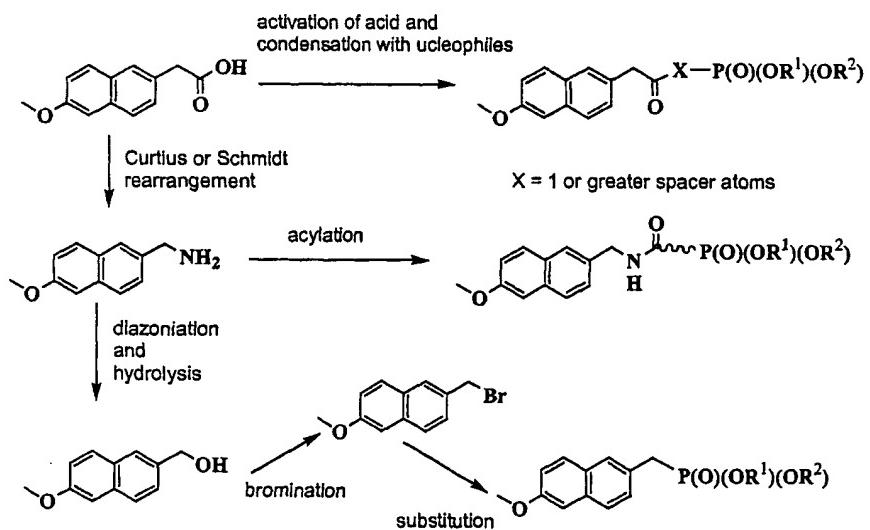


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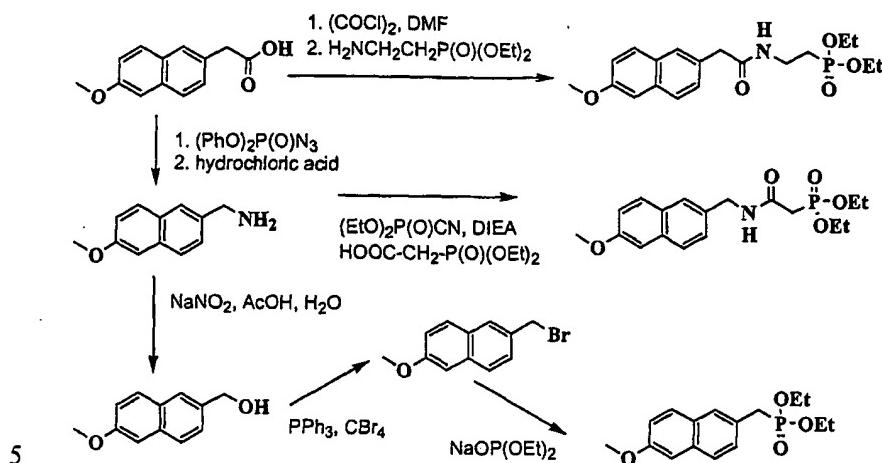
Zardaverine can be treated in a solvent such as DMF or THF with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The allylic bromide is then heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid.

Example 102 Preparation of Representative Compounds of the Invention

Other specific compounds of the invention can be prepared as illustrated
5 above.

Example 103 Preparation of Representative Compounds of the Invention

Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

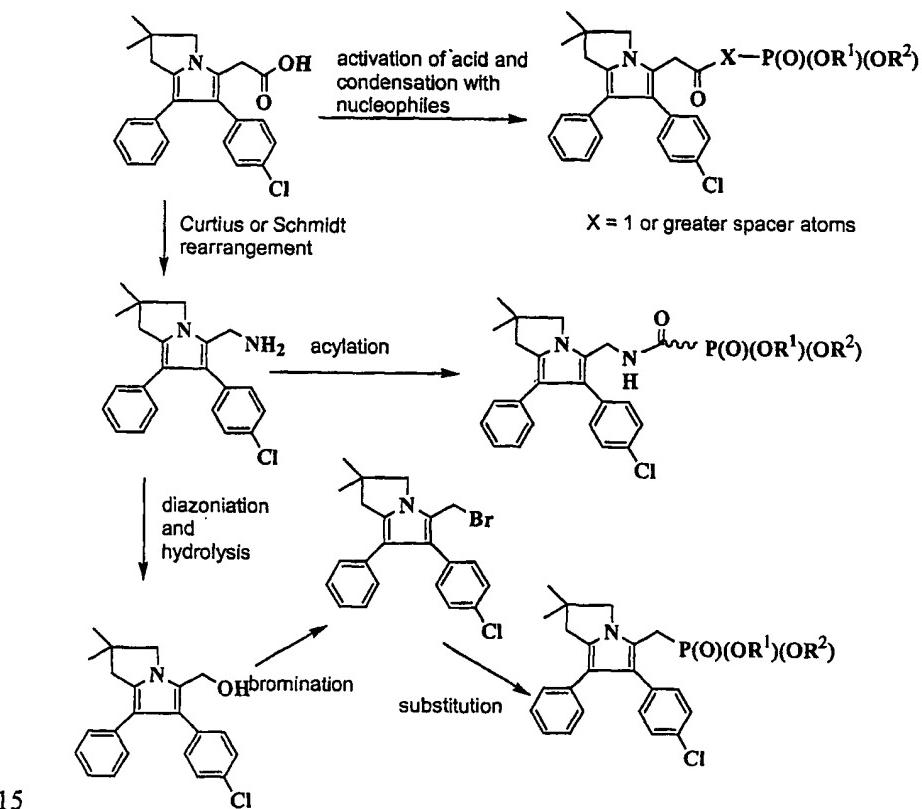


6-Methoxy-2-naphthylacetic acid, a major active metabolite of nabumetone (commercially available), can be converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then 10 coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

6-Methoxy-2-naphthylacetic acid can be treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as 15 triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-20 964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

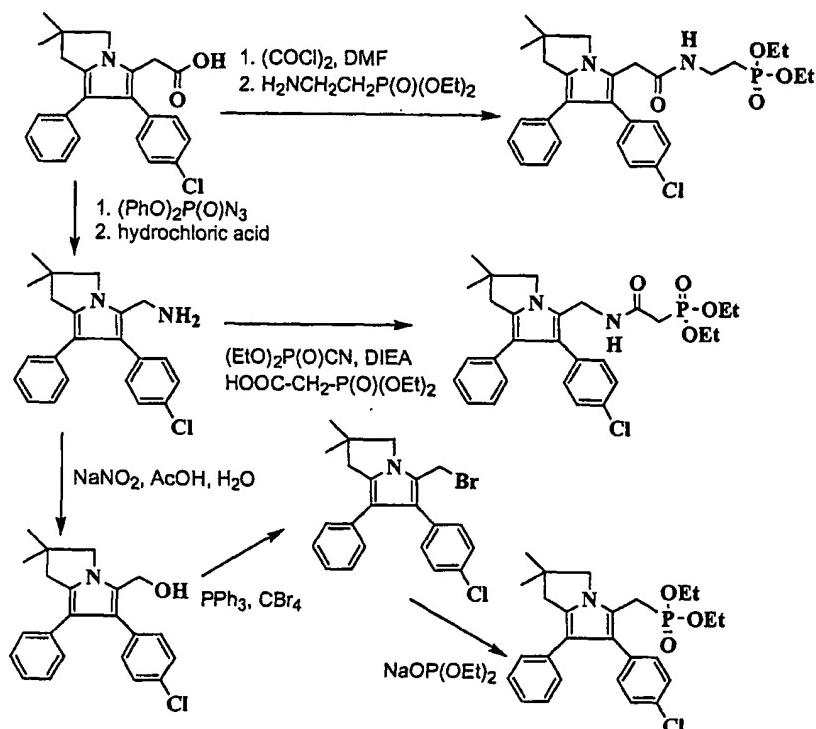
The amine derived from 6-methoxy-2-naphthylacetic acid can be converted to the alcohol, according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159. Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of nabumetone, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

Example 104 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

5



Licofelone is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-

- 10 aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

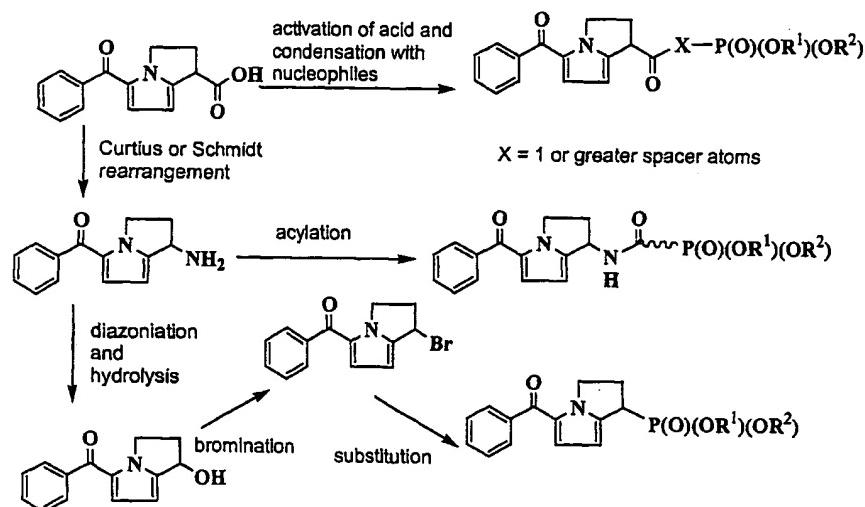
Licofelone is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*,

1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

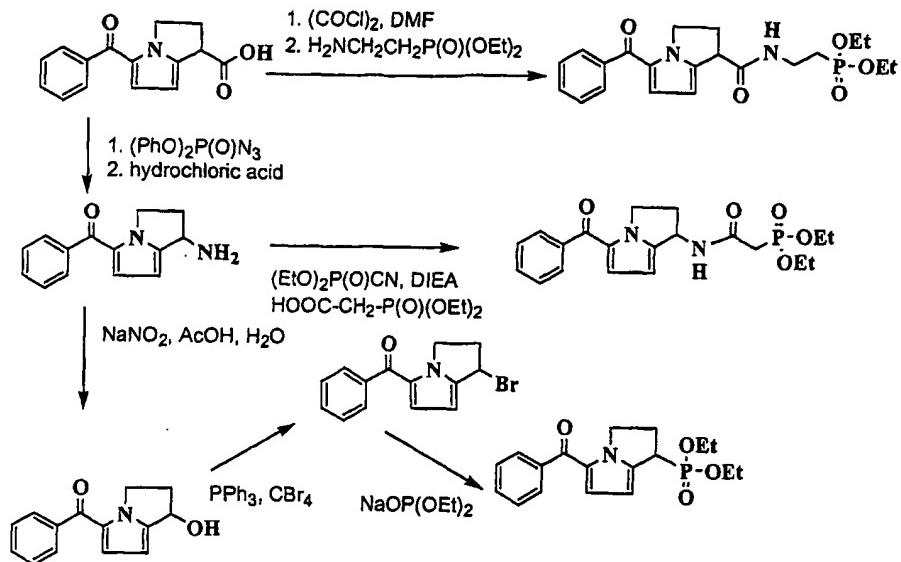
- 5 The amine derived from licofelone can be converted to the alcohol, according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159. Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with
- 10 triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of licofelone, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

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Example 105 Preparation of Representative Compounds of the Invention



- 20 Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.



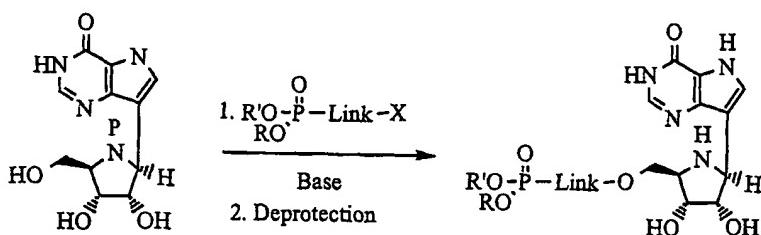
Ketorolac is converted to its acid chloride by treatment with oxalyl
 5 chloride in dimethylformamide. The acid chloride is then coupled with 2-
 aminoethylphosphonic acid diethyl ester in the presence of a base such as
 triethylamine in a solvent such as dichloromethane to generate the desired amide
 product.

- Ketorolac is treated in a solvent such as acetonitrile with
 10 diphenylphosphoryl azide in the presence of a base such as triethylamine at room
 temperature or up to reflux temperature. After cooling, the mixture is treated
 with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67,
 6260). The amine is then acylated with an activated diethylphosphonoacetic
 acid to provide the desired amide linker compound, according to a procedure
 15 such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*,
 1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained
 by treatment in a solvent such as dimethylformamide with a coupling reagent
 such as diethyl cyanophosphonate and a base such as diisopropylethylamine at
 room temperature.
- The amine derived from ketorolac can be converted to the alcohol,
 20 according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159.
 Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water,

to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of ketorolac, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

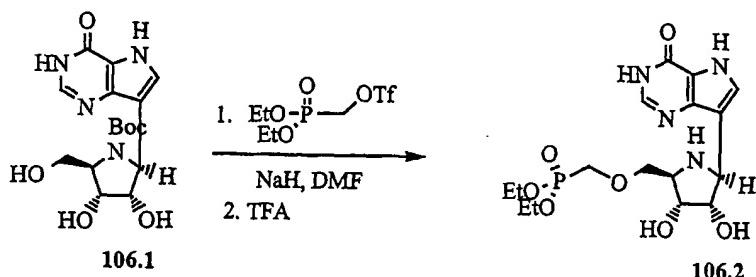
Example 106 Preparation of Representative Compounds of the Invention

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Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.



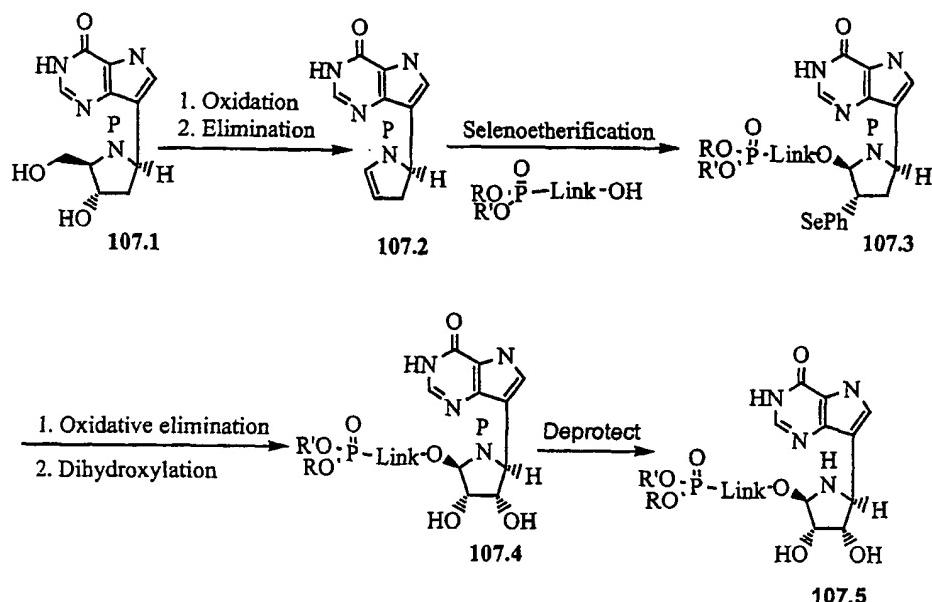
20

The Boc-protected (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-

D-ribitol, compound 106.1, is prepared by stirring the (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol (WO 9,919,338 and Evans, G. B. et al., *Tetrahedron*, 2000, 56, 3053, also reported in Evans, G. B. et al., *J. Med. Chem.* 2003, 46, 3412) with BOC anhydride as described in Greene, T., Protective groups in organic synthesis, Wiley-Interscience, 1999. Compound 106.1 is then

treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added, yielding the desired phosphonate diester 106.2 after deprotection 5 of the BOC group using trifluoroacetic acid (TFA).

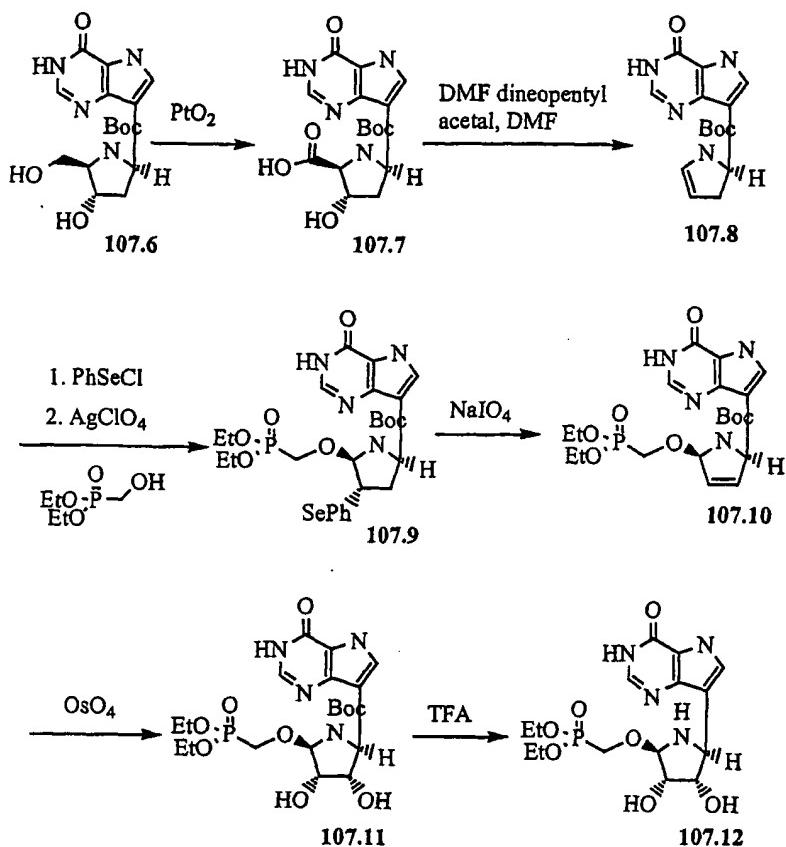
Example 107 Preparation of Representative Compounds of the Invention



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Representative compounds of the invention can be prepared as illustrated above. Deprotected compound 107.1 ((1R)-1-(9-deazahypoxanthin-9-yl)-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol, as the hydrochloride salt) is prepared as described in Evans, G. B. et al., *Tetrahedron*, 2000, 56, 3053, using di-*t*-butyl dicarbonate in dichloromethane. Oxidation of the 5'-OH followed by 15 elimination provides glycal 107.2 (see the procedure of Zemlicka J. et al., *J. Am. Chem. Soc.*, 1972, 94, 9, 3213). Selenoetherification provides the protected phosphonate 107.3 (Kim, C. et al., *J. Org. Chem.*, 1991, 56, 2642). Oxidative 20 elimination of the phenylselenide (as described in Kim, C. et al., *J. Org. Chem.*, 1991, 56, 2642) followed by stereoselective dihydroxylation provides the desired diol 107.4. Finally, the protecting group is removed to provide compound 107.5.

A specific compound of the invention can be prepared as follows.

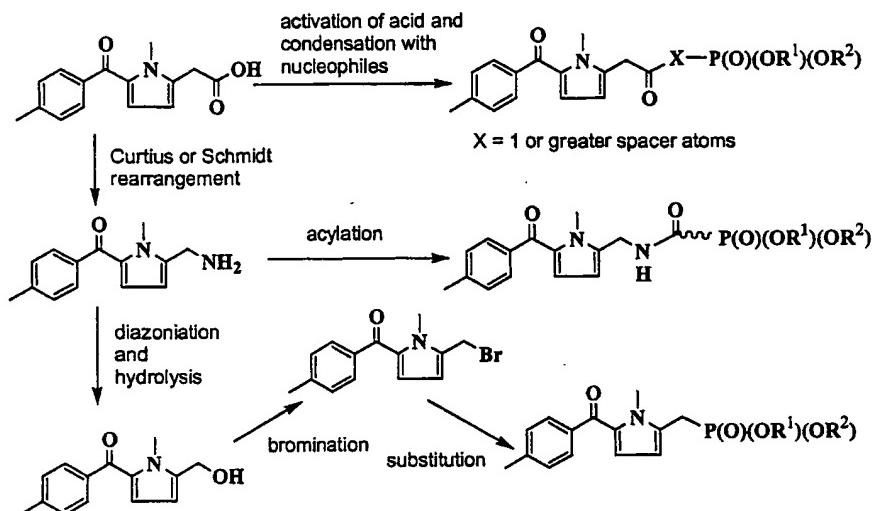


- Specifically, (1R)-1-(9-deazahypoxanthin-9-yl)-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol, prepared as the HCl salt as described in Evans, G. B. et al., *Tetrahedron*, 2000, 56, 3053, is first protected and then oxidized with PtO₂ to provide carboxylic acid 107.7. Decarboxylative elimination is achieved using dimethylformamide dineopentyl acetal in dimethylformamide at high temperature (Zemlicka J. et al., *J. Am. Chem. Soc.*, 1972, 94, 9, 3213).
- 10 Selenoetherification followed by treatment of the protected glycal with silver perchlorate in the presence of diethyl(hydroxymethyl)phosphonate (Phillion, D. et al., *Tetrahedron Lett.*, 1986, 27, 1477) provides the phosphonate 107.9 (Kim, C. et al., *J. Org. Chem.*, 1991, 56, 2642). Oxidative elimination of the selenide followed by dihydroxylation using osmium tetroxide provides diol 107.11.
- 15 Removal of the amine protecting group, according to the procedure of Greene,

T., Protective groups in organic synthesis, Wiley-Interscience, 1999, provides compound 107.12.

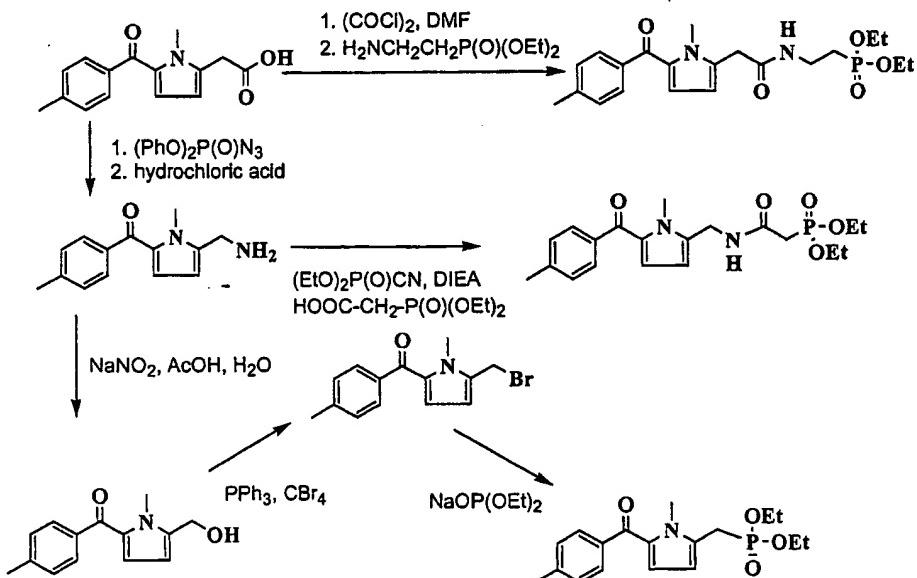
Example 108 Preparation of Representative Compounds of the Invention

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Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

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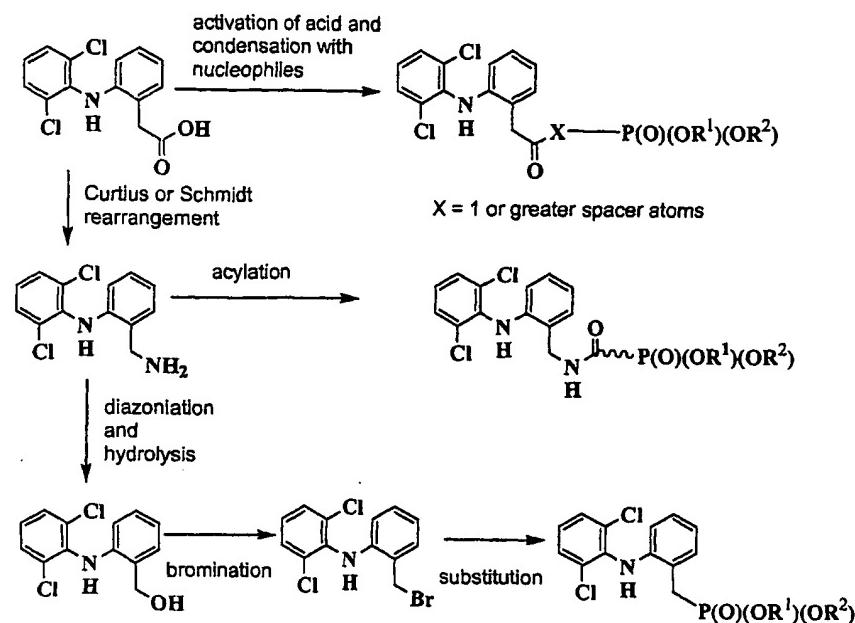


Tolmetine, an active metabolite of amtolmetine guacil, is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

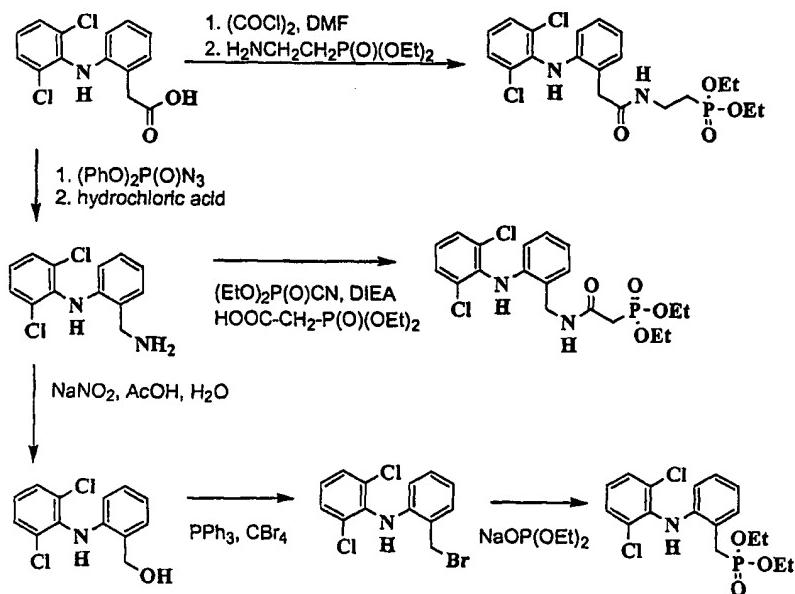
Tolmetine is treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid is obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The amine derived from tolmetine is converted to the alcohol according to the procedure reported in *J. Org. Chem.*, 1999, 64, 4159. Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of amtolmetine guacil, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

Example 109 Preparation of Representative Compounds of the Invention



5 Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

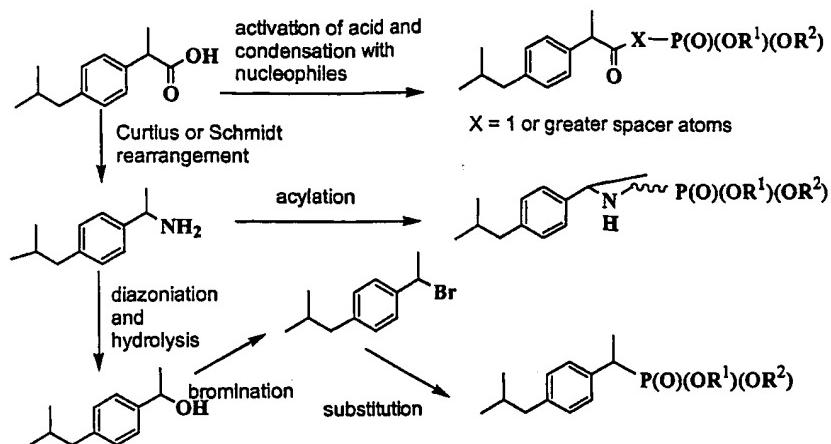


Diclofenac, a metabolite and a synthetic precursor of aceclofenac, can be converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-
5 aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired compound.

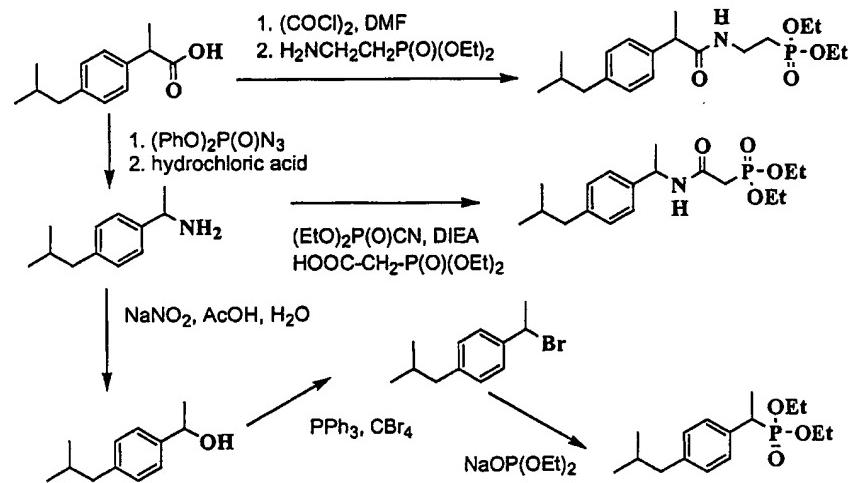
Diclofenac can be treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room
10 temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 15 1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The amine derived from diclofenac can be converted to the alcohol,
20 according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159. Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as
25 that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of aceclofenac, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

Example 110 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.

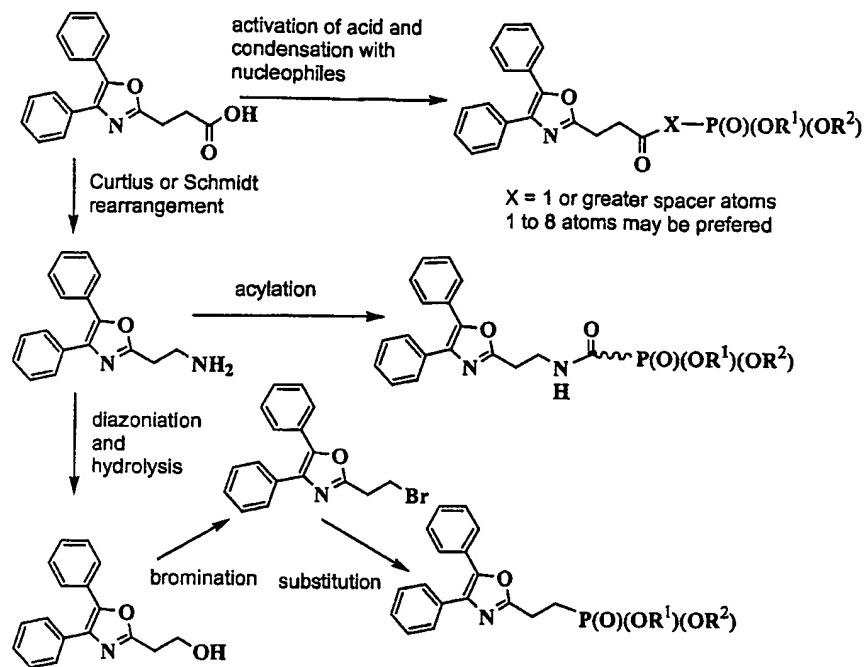


Ibuprofen, an active metabolite of metoxibutropate, can be converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

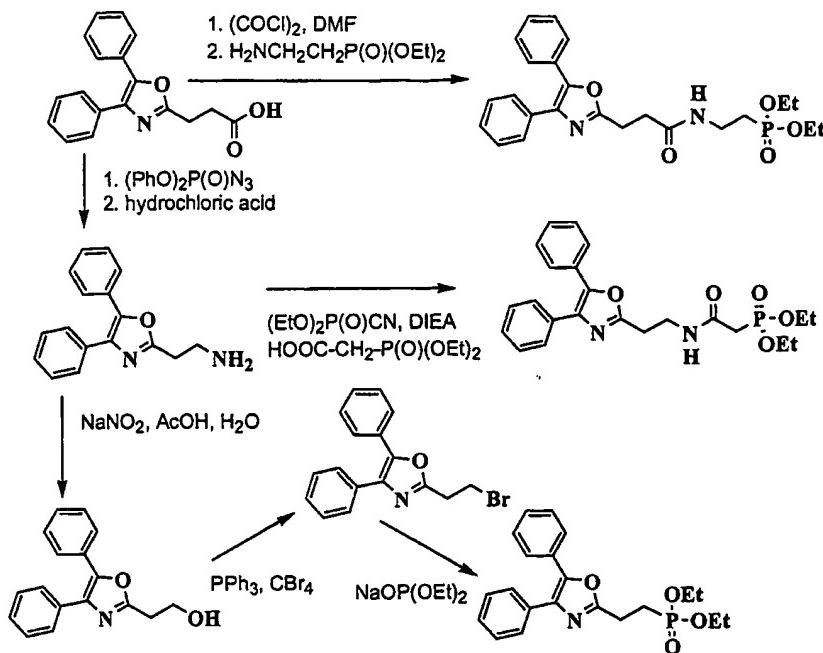
Ibuprofen can be treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 5 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent 10 such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

The amine derived from ibuprofen can be converted to the alcohol, according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159. Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, 15 to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester 20 to provide the desired phosphonate derivative of metoxibutropate, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

Example 111 Preparation of Representative Compounds of the Invention



5 Representative compounds of the invention can be prepared as illustrated above. For example, specific compounds of the invention can be prepared as follows.



Oxaprozin can be converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-

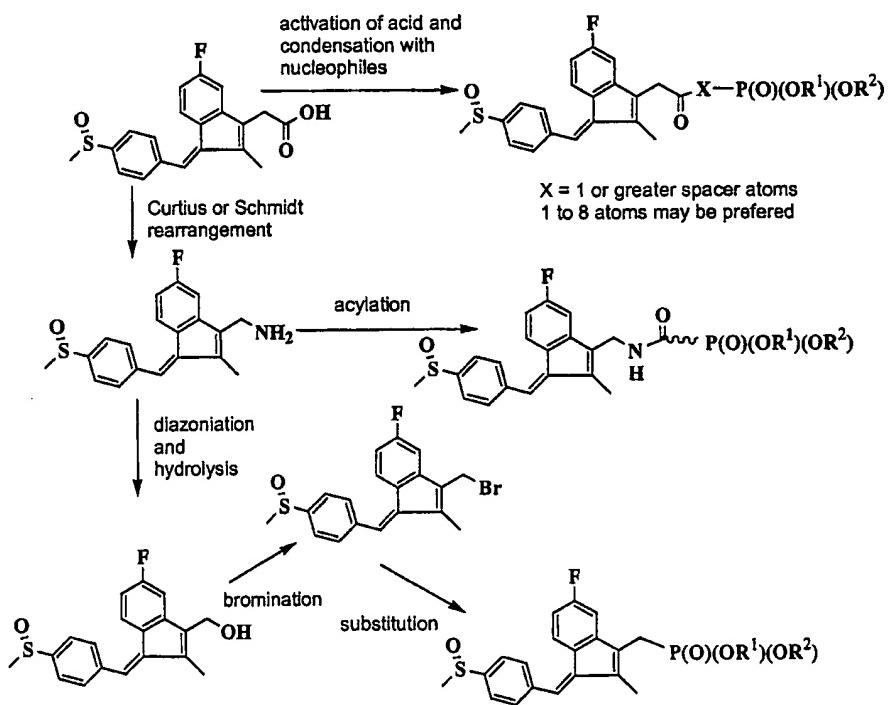
- 5 aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

Oxaprozin can be treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room 10 temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 15 1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

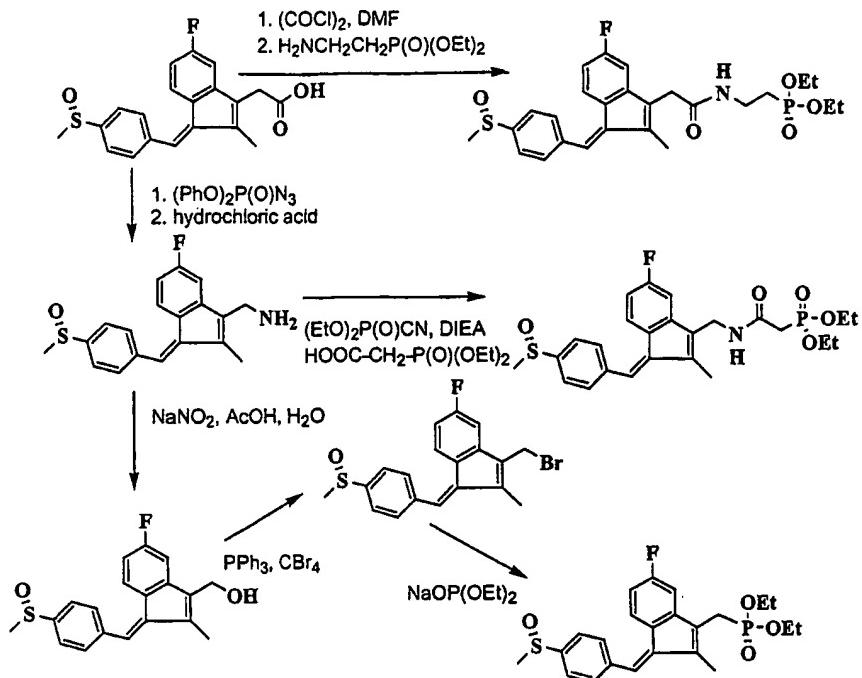
The amine derived from oxaprozin can be converted to the alcohol, 20 according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159.

Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as 5 that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of oxaprozin, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

10 Example 112 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated 15 above. For example, specific compounds of the invention can be prepared as follows.



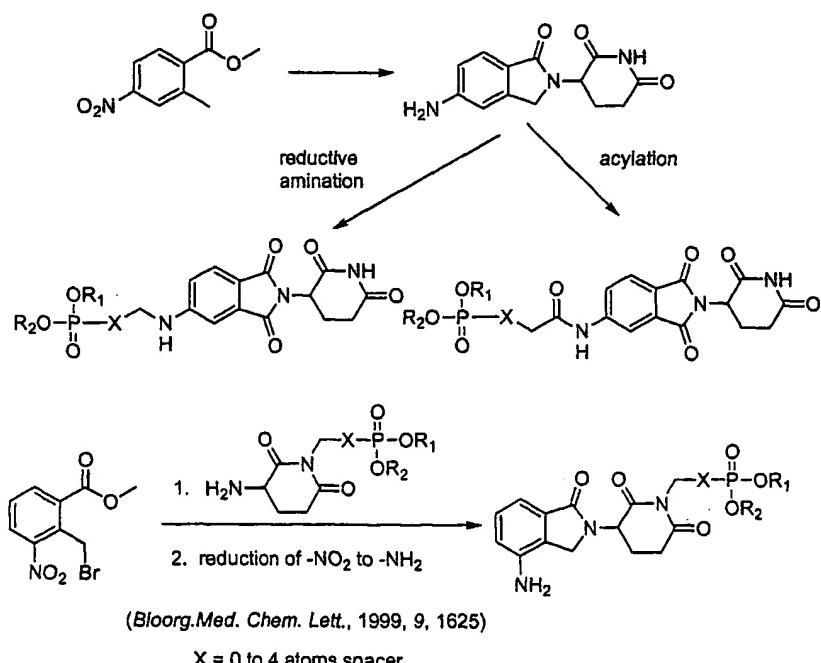
Sulindac can be converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

Sulindac can be treated in a solvent such as acetonitrile with diphenylphosphoryl azide in the presence of a base such as triethylamine at room temperature or up to reflux temperature. After cooling, the mixture is treated with diluted hydrochloric acid to provide the amine (*J. Org. Chem.*, 2002, 67, 6260). The amine is then acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

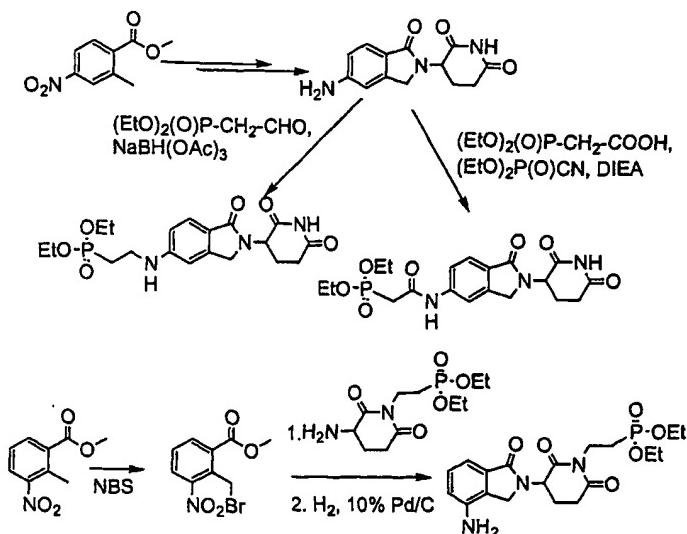
The amine derived from sulindac can be converted to the alcohol, according to a procedure such as that reported in *J. Org. Chem.*, 1999, 64, 4159.

Accordingly, the amine is dissolved in a mixed solvent of acetic acid and water, to which sodium nitrite in water is added dropwise to afford the desired alcohol. The alcohol is then converted to the bromide by treatment with triphenylphosphine and tetrabromomethane, according to a procedure such as 5 that described in *J. Org. Chem.*, 2002, 67, 7215. The bromide is treated in a solvent such as tetrahydrofuran with sodium salt of phosphonic acid diethyl ester to provide the desired phosphonate derivative of sulindac, according to a procedure such as that reported in *Tetrahedron*, 1996, 52, 4411.

10 Example 113 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated 15 above. For example, specific compounds of the invention can be prepared as follows.



2-Methyl-4-nitrobenzoic acid methyl ester (commercially available) is converted to 3-(5-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione,

5 following the procedures reported in *Bioorg. Med. Chem. Lett.*, 1999, 9, 1625.

This amine intermediate is subjected to a reductive amination with diethylphosphonoacetaldehyde (obtained from ozonolysis of diethyl allylphosphonate) in the presence of a reducing agent such as sodium triacetoxyborohydride to generate the desired amine linker analog (*J. Org. Chem.*, 1996, 61, 3849).

10 Alternatively, the amine is acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960 and *J. Med. Chem.*, 1984, 27, 600. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a

15 coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

2-Methyl-3-nitrobenzoic acid methyl ester (commercially available) is treated in a solvent such as carbon tetrachloride with N-bromosuccinimide under light to produce 2-bromomethyl-3-nitrobenzoic acid methyl ester. This benzylic

20 bromide is treated in a solvent such as dimethylformamide with [2-(3-amino-2,6-dioxo-piperidin-1-yl)-ethyl]-phosphonic acid diethyl ester (for the preparation of this compound , see below) in the presence of a base such as triethylamine. The

coupled product is then reduced by hydrogenation (*Bioorg. Med. Chem. Lett.*, 1999, 9, 1625) to afford the desired analog.

[2-(3-Amino-2,6-dioxo-piperidin-1-yl)-ethyl]-phosphonic acid diethyl ester is obtained according to a procedure such as that reported in *J. Med. Chem.*,

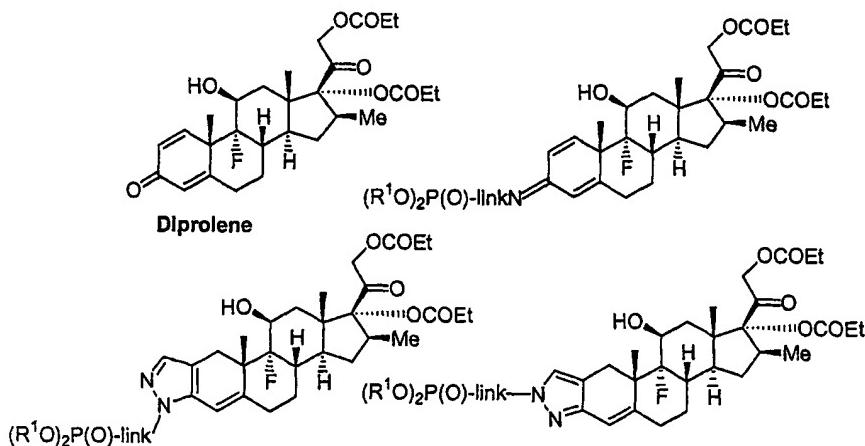
- 5 2003, 46, 3793. Accordingly, benzyloxycarbonyl-protected glutaric acid is treated in a solvent such as acetonitrile with triethylamine, 1-hydroxy-benzotriazole, diethyl 2-aminoethyl-phosphonate and 1,3-dicyclohexyl-carbodiimide. After the reaction is complete, the solvent is removed and the residue is purified by chromatography to generate the cyclic product, which is
10 subjected to hydrogen in the presence of palladium catalysis to afford the desired intermediate.

Examples 114-117 – Diproline Derivatives

The structures of Diprolene (German Patent DE 2905674) and

- 15 representative diproline phosphonate derivatives of the invention are shown below, in which the substituent R¹ is H, alkyl, alkenyl, aryl or aralkyl. The derivatives incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.

20

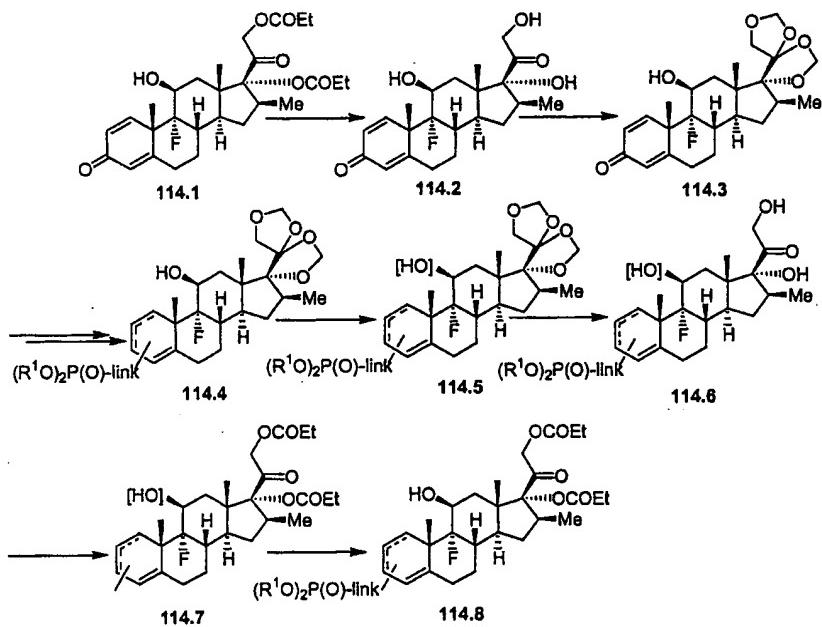


The synthesis of representative phosphonate derivatives of diproline is outlined in Examples 114-117. In these Examples, it may be necessary to protect certain

reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

10

Example 114 Preparation of Representative Diprolone Derivatives



15 The steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, the propionate esters are hydrolyzed, for example by reaction with two molar equivalents of lithium hydroxide in aqueous dimethoxyethane solution at ambient temperature, to give the diol 114.2. The product is then reacted with paraformaldehyde and an acid catalyst such as 20 hydrochloric acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the

BMD derivative **114.3**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester **114.4**. Prior to hydrolysis of the BMD protecting group, the 11-hydroxyl group is protected.

The protecting group is selected so that it is stable to the conditions required for removal of the BMD group, and so that it is removable without affecting the subsequently introduced 17, 21-diester moiety. For example, the 11-hydroxyl group is protected by conversion to the 4-azidobutyrate ester, by reaction with 4-azidobutyryl chloride in pyridine. The 11-azidobutyrate group is then removed from the diester **114.7** by reaction with triphenylphosphine, as described in Bull.

- 5 Soc. Chem. Jpn., 59, 1296, 1986. Alternatively, the 11-hydroxyl group is protected by conversion to the 2-(trimethylsilyl)ethyl carbonate, by reaction with 2-(trimethylsilyl)ethyl carbonyl chloride and pyridine. The 2-(trimethylsilyl) carbonate is removed from the diester **114.7** by reaction with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in Tet. Lett., 22, 969, 1981.

10 Alternatively, the 11-hydroxyl group is protected by conversion to the trichloroacetyl ester, by reaction with trichloroacetyl chloride in dimethylformamide-pyridine. The trichloroacetyl ester is removed by reaction with ethanolic ammonia at ambient temperature, as described in Coll. Czech.

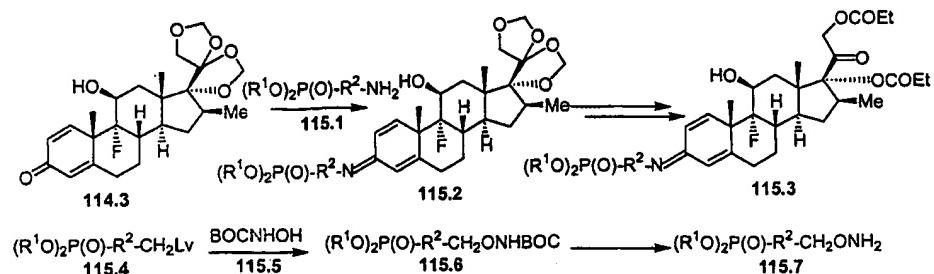
- 15 20 Chem. Commun., 27, 2567, 1962.

The BMD moiety in the protected product **114.5** is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the diol **114.6**; the latter compound is then

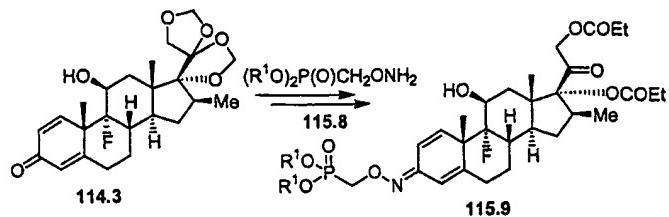
- 25 acylated, for example by reaction with propionic acid and dicyclohexyl carbodiimide in dimethylformamide at ambient temperature, or by reaction with propionyl chloride and triethylamine in dichloromethane, to produce the dipropionate **114.7**. Deprotection of the 11-hydroxyl group, as described above, then affords the diester **114.8**.

- 30 Alternatively, the 20-ketone group is protected as the diethylamine adduct by reaction with titanium tetrakis(diethylamide), as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 219.

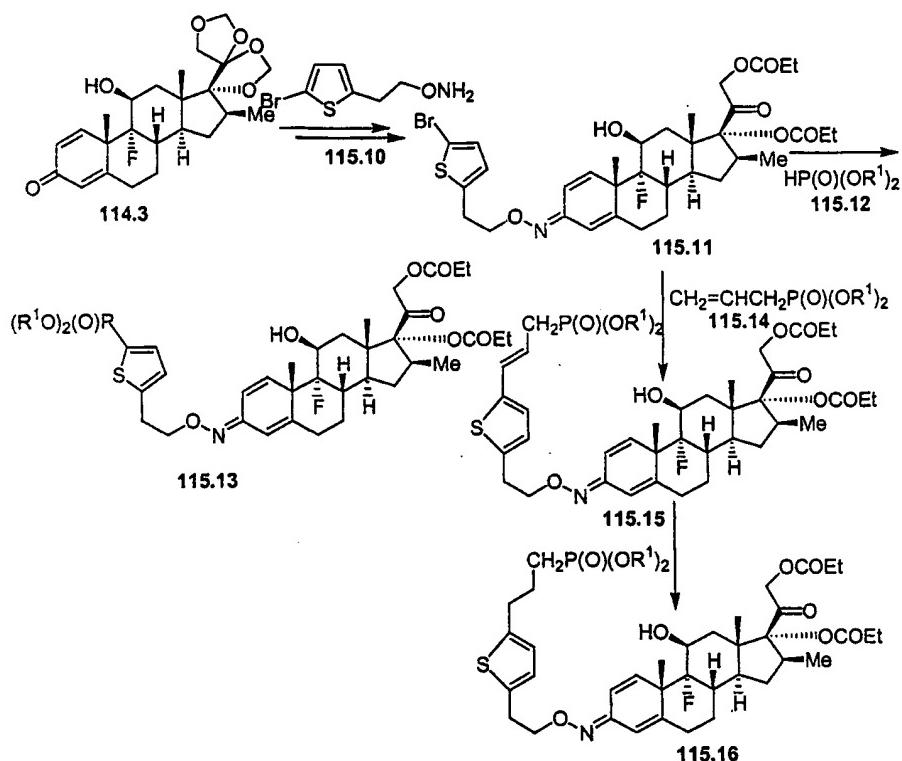
Example 115 Preparation of Representative Diproline Derivatives



- 5 The preparation of phosphonate derivatives of diproline in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative **114.3** is reacted with an amine or hydroxylamine **115.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, to afford the imine or iminoxy product **115.2**. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an
10 alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in Anal. Bioch., 1978, 86, 133. and in J. Mass. Spectrom., 1995, 30, 497. The BMD-protected compound **115.2** is then converted, as described in example 114 into the diester **115.3**.
- 15 The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate **115.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine **115.5** (Aldrich) to produce the ether **115.6**. The reaction is conducted between equimolar amounts of the reactants in a polar
20 solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine, to give the product **115.6**. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether **115.7**.
- 25



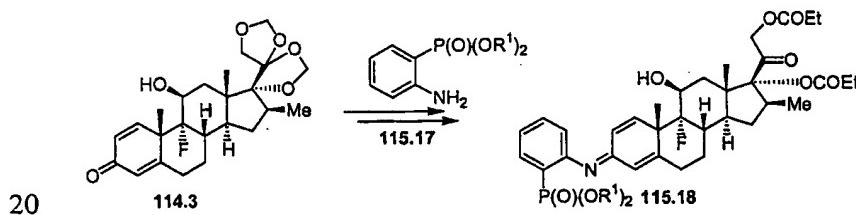
The preparation of phosphonate derivatives of diproline in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate 114.3 is reacted with a dialkyl phosphonomethyl hydroxylamine 115.8, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (Tet. Lett., 1986, 27, 1477) and BOC-hydroxylamine, to afford, after deprotection and side chain acylation, the oxime ether 115.9. The oxime forming reaction is performed at ambient temperature in pyridine solution between equimolar amounts of the reactants. Using the above procedures, but employing, in place of the oxime ether 115.8, different oxime ethers 115.7, the corresponding products 115.3 are obtained.



The preparation of phosphonate derivatives of diproline incorporating an iminoxy group, by means of the reaction between the substrate 114.3 and O-2-(5-bromo-2-thienyl)ethoxyhydroxylamine 115.10, prepared as described above from 2-(5-bromo-2-thienyl)ethyl bromide (J. Chem. Soc., Perkin Trans. Phys. Org. Chem., 1975, 821) is illustrated above. The resultant oxime ether is converted, by deprotection and side chain acylation, into the compound 115.11 which is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite 115.12 to afford the phosphonate 115.13. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

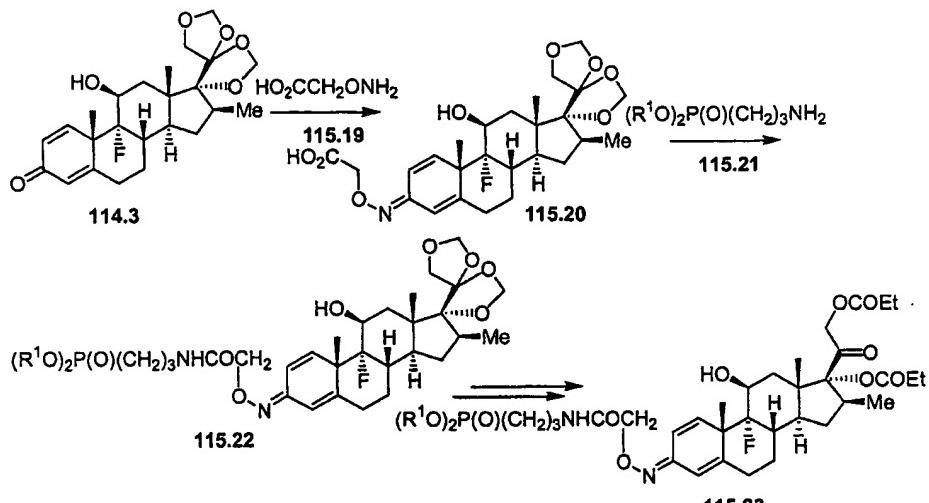
Alternatively, the bromo-substituted product 115.11 is coupled, in a palladium-catalyzed Heck reaction, with a dialkyl propenyl phosphonate 115.14 (Acros) to give the unsaturated phosphonate 115.15. The coupling of aryl halides

- with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 115.15 is reduced, for example by reaction with diimide, to produce the saturated analog 115.16. The reduction of olefinic bonds is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.
- Using the above procedures, but employing, in place of the bromothienyl reagent 115.10, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 115.13, 115.15 and 115.16 are obtained.



- The preparation of phosphonate derivatives of diprolin in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate 114.3 is reacted with a dialkyl 2-aminophenyl phosphonate 115.17 (Aurora) to give, after deprotection and side chain acylation, the imine product 115.18. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions, to give the product 115.18.

Using the above procedures, but employing, in place of the 2-aminophenyl phosphonate **115.17**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **115.18** are obtained.



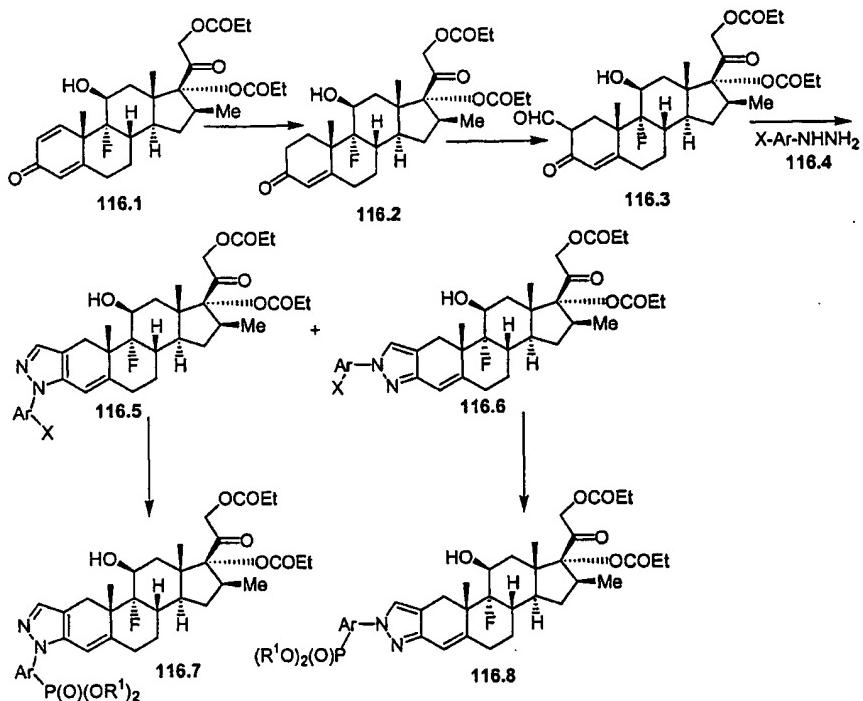
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An alternative method for the preparation of phosphonate derivatives in which the phosphonate is attached by means of an oximino group is illustrated above. In this procedure, the dienone **114.3** is reacted with O-(carboxymethyl)hydroxylamine **115.19** (Interchim) to yield, after deprotection and side chain acylation, the oxime **115.19**. The reaction of steroidal 1,4-dien-3-ones with hydroxylamine is described in J. Steroid Bioch., 1976, 7, 795. The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime **115.20** is then reacted with a dialkyl 3-hydroxyphenyl phosphonate **115.21** (Epsilon) in a Mitsonobu reaction, to yield the substituted oxime **115.22**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol and the hydroxy or mercapto component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a

triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The product **115.22** is then transformed, by deprotection and acylation, into the diester **115.23**.

Using the above procedures, but employing, in place of the phosphonate **115.22** different dialkyl hydroxy-substituted aryl or heteroaryl phosphonates, the products analogous to **115.23** are obtained.

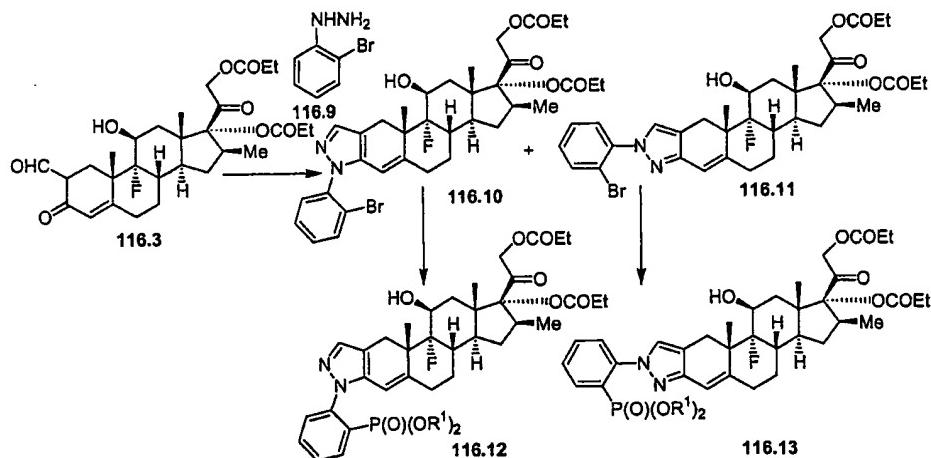
Example 116 Preparation of Representative Diproline Derivatives



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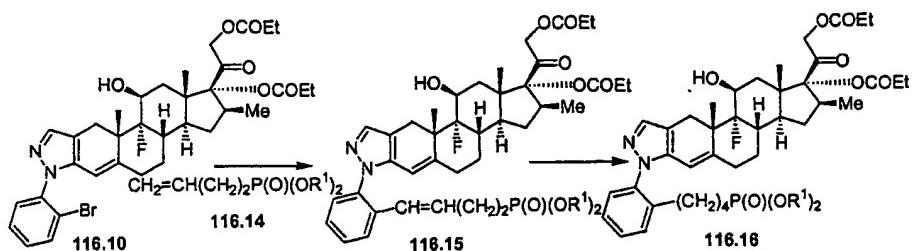
The preparation of phosphonate esters of diproline in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, Diprolene **116.1** is reduced to afford the 1,2-dihydro product, **116.2**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in J. Med. Chem., 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in Australian Patent Application

275950409, to afford the 2-formyl product **116.3**. Optionally, the substrate **116.1** is protected, for example as described in example 114, prior to the formylation reaction, as described in J. Am. Chem. Soc., 1964, 86, 1520. The 2-formyl product is then reacted with an aryl or heteroaryl hydrazine **116.4**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles **116.5** and **116.6**. The ring-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in J. Am. Chem. Soc., 1964, 86, 1520. The pyrazoles **116.5** and **116.6** are then transformed, respectively into the phosphonates **116.7** and **116.8**.

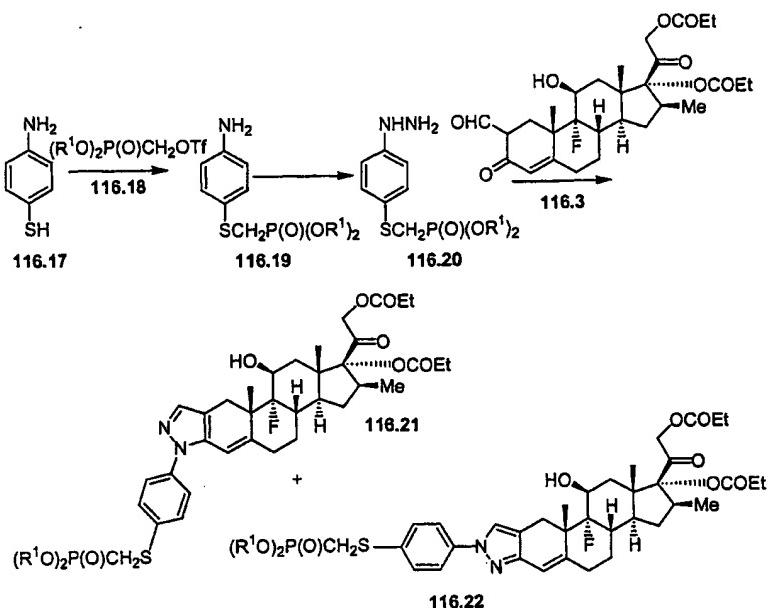


15

The preparation of phosphonate derivatives of diproline in which the phosphonate is attached by means of a phenyl group is illustrated above. In this sequence, the ketoaldehyde **116.3** is reacted, as described above, with 2-bromophenylhydrazine **116.9** (Fluka), to give the isomeric pyrazole products **116.10** and **116.11**. The products are then reacted, as described above, with a dialkyl phosphite $\text{HP}(\text{O})(\text{OR}')_2$ and a palladium catalyst, to afford respectively the phosphonates **116.12** and **116.13**. Using the above procedures, but employing, in place of 2-bromophenyl hydrazine, different bromoaryl or bromoheteroaryl hydrazines **116.4**, the products **116.7** and **116.8** are obtained.

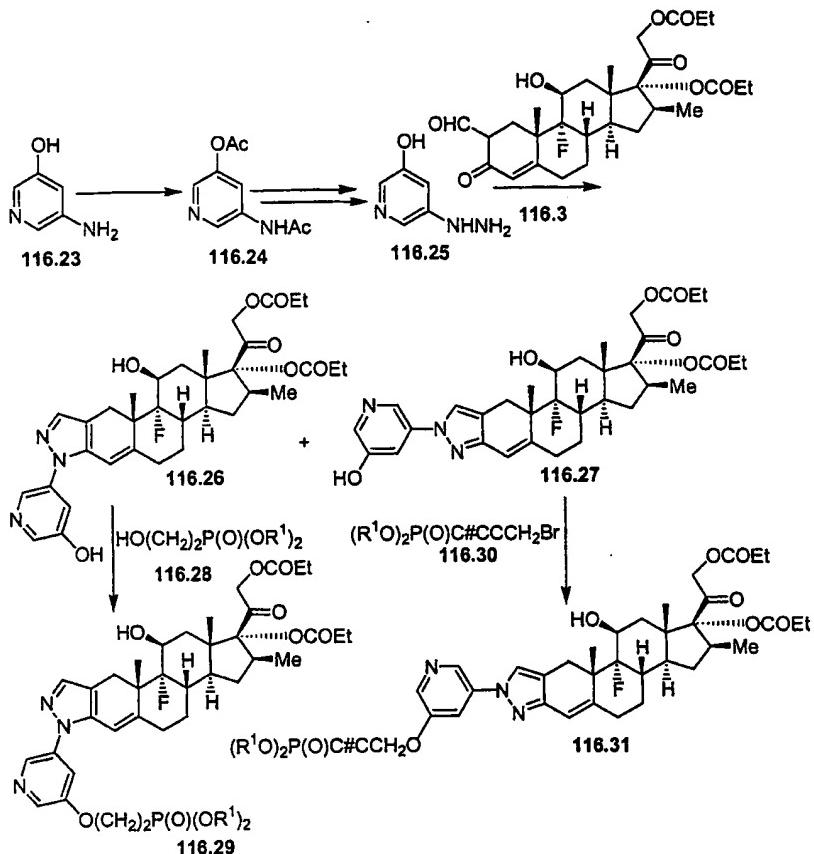


- The preparation of phosphonate diproline derivatives in which the
- 5 phosphonate is attached by means of an aromatic or heteroaromatic group and a saturated or unsaturated alkyl chain is illustrated above. In this procedure, the bromophenyl-substituted pyrazole 116.10 is coupled in a Heck reaction, as described above, with, for example a dialkyl butenyl phosphonate 116.14 (Org. Lett., 2001, 3, 217) to give the unsaturated phosphonate product 116.15.
- 10 Optionally, the product is reduced, as described above, to give the saturated analog 116.16. Application of the above procedures to the isomeric bromophenyl pyrazole 116.11 affords the products isomeric with 116.15 and 116.16. Using the above procedures, but employing, in place of the phosphonate 116.14, different dialkyl alkenyl phosphonates, and/or different bromoaryl or heteroaryl
- 15 pyrazoles 116.5 or 116.6, the products analogous to 116.15 and 116.16 are obtained.



The preparation of phosphonate diproline derivatives in which the phosphonate is attached by means of an aryl or heteroaryl group and an alkoxy chain is illustrated above. In this procedure, 4-aminothiophenol **116.17** is reacted in dimethylformamide solution at ambient temperature with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **116.18** (*Tet. Lett.*, 1986, 27, 1477) and potassium carbonate to give the thioether **116.19**. The product is then converted into the corresponding hydrazine **116.20** by means of a diazotization reaction in aqueous ethanolic hydrochloric acid, followed by reduction of the diazonium chloride with tin(II) chloride, as described in *J. Med. Chem.*, 2001, 44, 4031. The hydrazine is then reacted, as described above, with the ketoaldehyde **116.3**, to form the isomeric pyrazoles **116.21** and **116.22**.

Using the above procedures, but employing, in place of the triflate **116.18**, different dialkylphosphono alkyl bromides or triflates, and/or different aromatic or heteroaromatic mercapto or hydroxyamines, the products analogous to **116.21** and **116.22** are obtained.

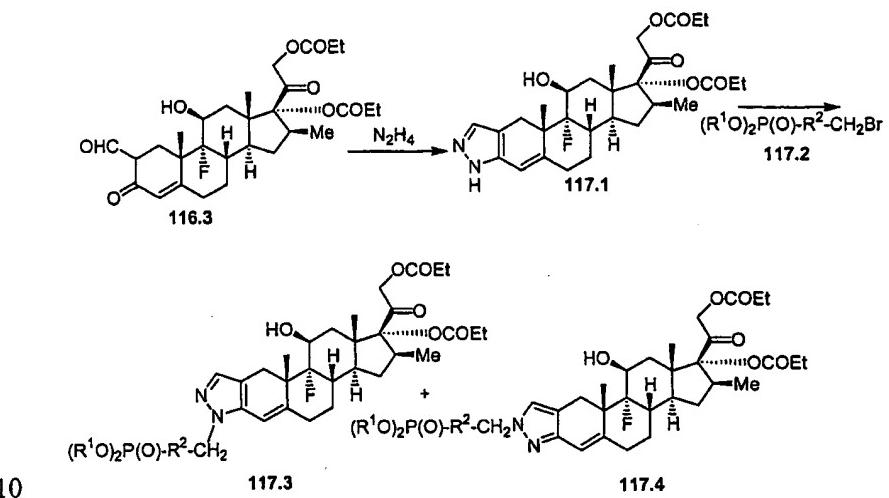


The preparation of phosphonate diprolone derivatives in which the phosphonate is attached by means of a pyridyl group a heteroatom and a variable carbon chain is illustrated above. In this procedure, 3-amino-5-hydroxypyridine is converted, by reaction with acetic anhydride, into the diacetyl analog 116.24. The product is then transformed by diazotization and reduction, as described above, into the hydrazine 116.25. The hydrazine is then reacted with the ketoaldehyde 116.3 to give the isomeric pyrazoles 116.26 and 116.27. The 2'-pyridyl product 116.26 is reacted in a Mitsonobu reaction, as described above, with a dialkyl hydroxyethyl phosphonate 116.28 (Zh. Obschei. Khim., 1973, 43, 2364) to afford the ether 116.29. Application of this procedure to the isomeric phenol 116.27 affords the product isomeric to 116.29.

Alternatively, the isomeric phenol 116.27 is reacted, in dimethylformamide solution at about 80°, with one molar equivalent of a dialkyl bromopropynyl phosphonate 116.30 (Bioorg. Med. Chem. Lett., 1994, 4, 273)

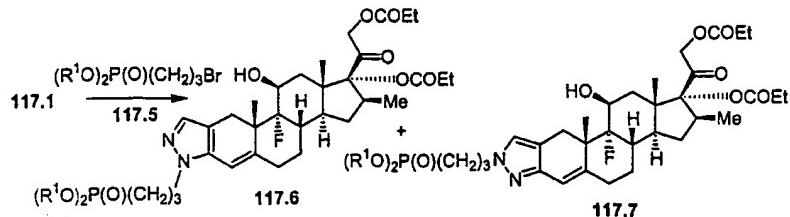
and cesium carbonate, to prepare the phosphonate **116.31**. Application of this procedure to the isomeric phenol **116.26** affords the product isomeric with **116.31**. Using the above procedures, but employing, in place of the carbinol **116.28** or the bromide **116.30**, different thiols, alcohols or bromides, and/or 5 different phenols **116.5** or **116.6** in which X is OH, the corresponding products analogous to **116.29** and **116.31** are obtained.

Example 117 Preparation of Representative Diproline Derivatives

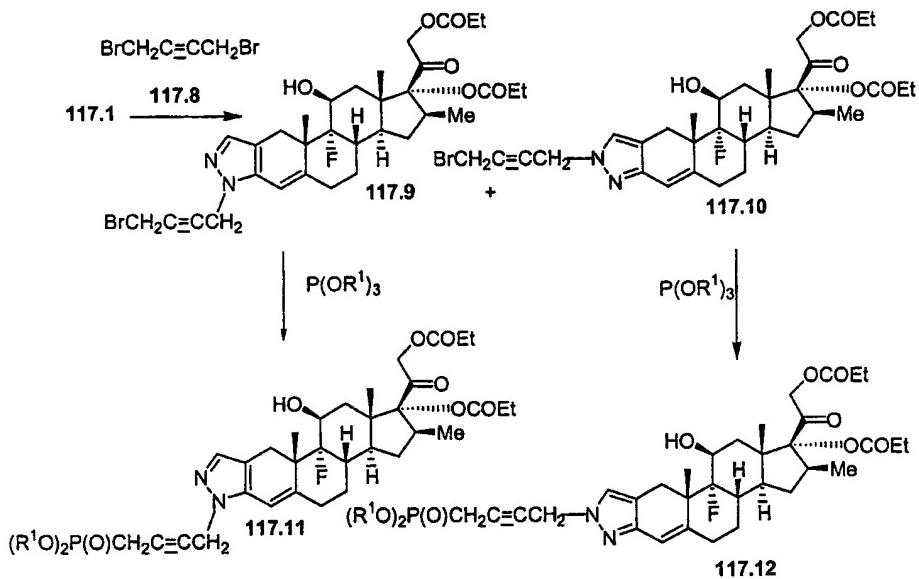


10

The preparation of the phosphonate diproline derivatives in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde **116.3** is reacted with 15 hydrazine, to afford the pyrazole derivative **117.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in J. Am. Chem. Soc, 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The resulting pyrazole is then reacted with a dialkyl bromomethyl phosphonate **117.2**, in which R^2 is as defined above, to produce the isomeric 2' and 1' 20 alkylation products **117.3** and **117.4** respectively. The alkylation of substituted pyrazoles is described, for example, in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 309.



Representative diproline derivatives of the invention can be prepared as illustrated above. The pyrazole 117.1 is reacted, in dimethylformamide solution at ca. 90°, with a dialkyl bromopropyl phosphonate 117.5 (Aldrich) and a base such as dimethylaminopyridine or lithium hexamethyldisilazide, to yield the isomeric alkylation products 117.6 and 117.7.



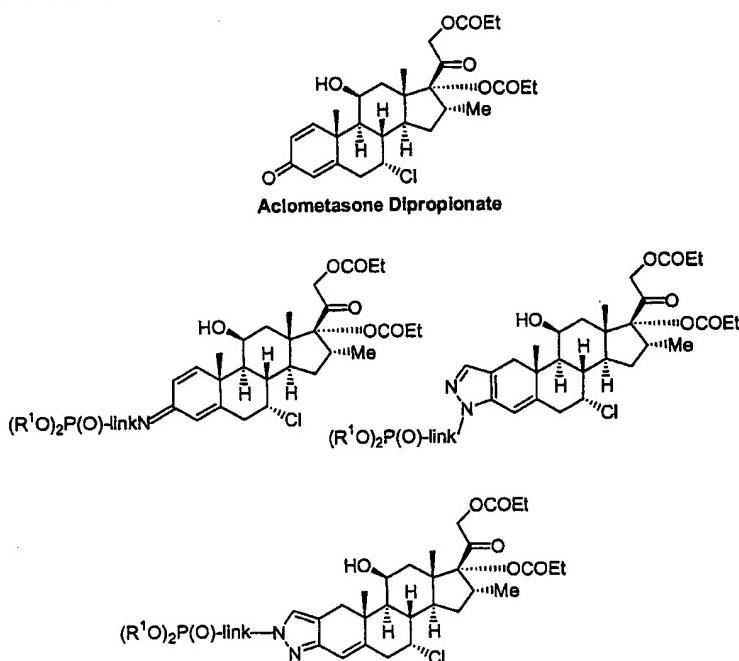
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Representative diproline derivatives of the invention can be prepared as illustrated above. The pyrazole 117.1 is reacted in dimethylformamide solution at ambient temperature with one molar equivalent of 1,4-dibromobut-2-yne 117.8 (Narchem) and potassium carbonate, to afford the alkylation products 117.9 and 117.10. The products are then heated at 120° with a trialkyl phosphite in an Arbuzov reaction, to yield the phosphonates 117.11 and 117.12. The Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115-72. Using the above procedures, but employing, in place of the dibromide 117.8,

different alkyl, alkenyl or alkynyl dibromides, the products analogous to 117.11 and 117.12 are obtained.

Examples 118-121 – Aclometazone Derivatives

5 The structures of Aclometasone dipropionate (*J. Med. Chem.*, 1980, 23, 430; US Patent 4124707) and representative phosphonate esters of the invention are shown below, in which the substituent R¹ is H, alkyl, alkenyl, aryl or aralkyl. These compounds incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the
10 attached structures.

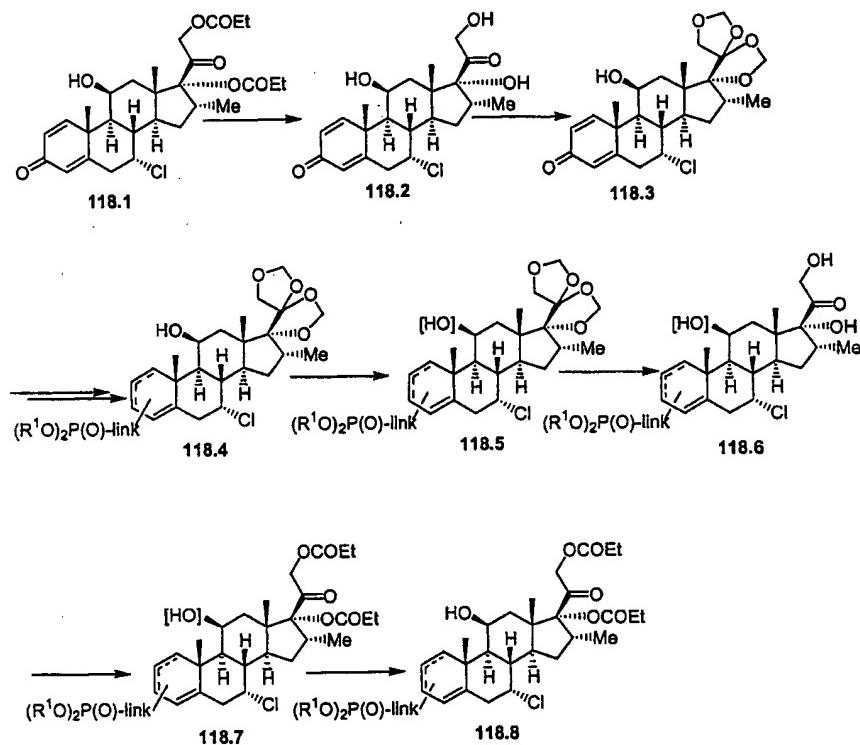


The synthesis of representative phosphonate derivatives of the invention is outlined in Examples 118-121. In these Examples, it may be necessary to
15 protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The
20 protection and deprotection of steroidal ketones and alcohols is described in

Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

5

Example 118 Preparation of Representative Aclometasone Derivatives



10

As illustrated above, a protection-deprotection sequence in which the steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, the propionate esters are hydrolyzed, for example by reaction with two molar equivalents of lithium hydroxide in aqueous dimethoxyethane solution at ambient temperature, to give the diol 118.2. The product is then reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative 118.3. The phosphonate moiety is then introduced, using the procedures described below, to

15

produce the phosphonate ester 118.4. Prior to hydrolysis of the BMD protecting group, the 11-hydroxyl group is protected. The protecting group is selected so that it is stable to the conditions required for removal of the BMD group, and so that it is removable without affecting the subsequently introduced 17, 21-diester moiety.

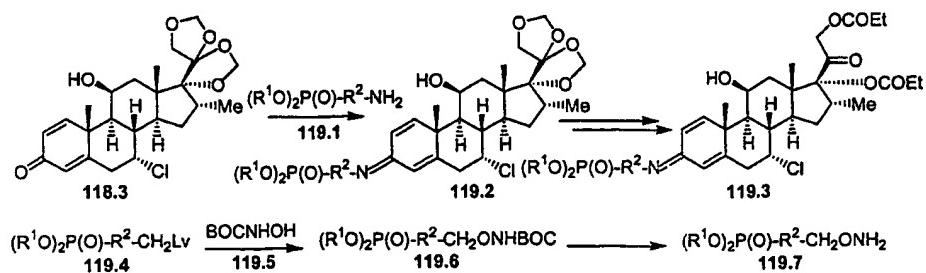
- 5 For example, the 11-hydroxyl group is protected by conversion to the 4-azidobutyrate ester, by reaction with 4-azidobutyryl chloride in pyridine. The 11-azidobutyrate group is then removed from the diester 118.7 by reaction with triphenylphosphine, as described in Bull. Soc. Chem. Jpn., 59, 1296, 1986.
- 10 Alternatively, the 11-hydroxyl group is protected by conversion to the 2-(trimethylsilyl)ethyl carbonate, by reaction with 2-(trimethylsilyl)ethyl carbonyl chloride and pyridine. The 2-(trimethylsilyl) carbonate is removed from the diester 118.7 by reaction with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in Tet. Lett., 22, 969, 1981.

- 15 Alternatively, the 11-hydroxyl group is protected by conversion to the trichloroacetyl ester, by reaction with trichloroacetyl chloride in dimethylformamide-pyridine. The trichloroacetyl ester is removed by reaction with ethanolic ammonia at ambient temperature, as described in Coll. Czech. Chem. Commun., 27, 2567, 1962.

- 20 The BMD moiety in the protected product 118.5 is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the diol 118.6; the latter compound is then acylated, for example by reaction with propionic acid and dicyclohexyl carbodiimide in dimethylformamide at ambient temperature, or by reaction with 25 propionyl chloride and triethylamine in dichloromethane, to produce the dipropionate 118.7. Deprotection of the 11-hydroxyl group, as described above, then affords the diester 118.8.

- 30 Alternatively, the 20-ketone group is protected as the diethylamine adduct by reaction with titanium tetrakis(diethylamide), as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 219.

Example 119 Preparation of Representative Aclometasone Derivatives

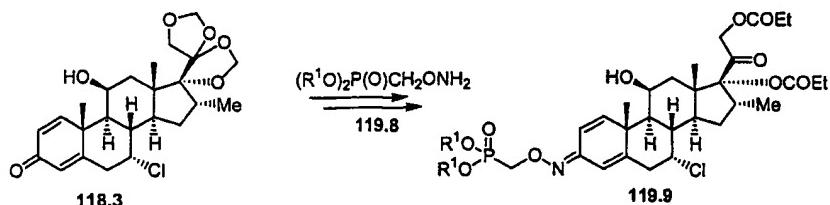


The preparation of phosphonate derivatives of Aclometasone in which

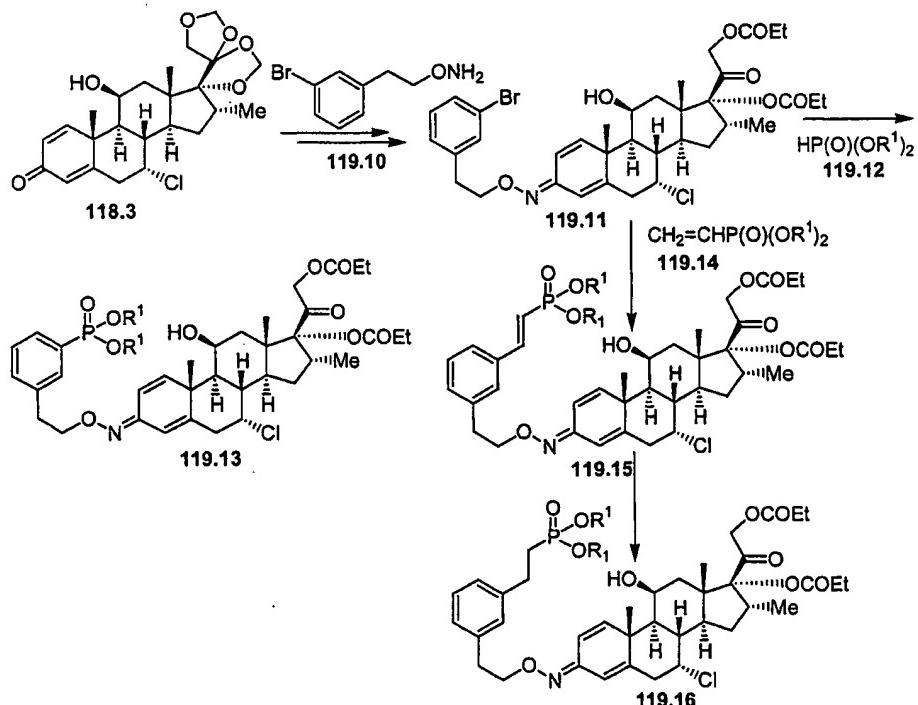
- 5 the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative 118.3 is reacted with an amine or hydroxylamine 119.1, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, to afford the imine or iminoxy product 119.2. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst to
- 10 give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in Anal. Bioch., 1978, 86, 133. and in J. Mass. Spectrom., 1995, 30, 497. The BMD-protected side-chain compound 119.2 is then converted, as described in Example 118 into the diester 119.3.
- 15

The preparation of hydroxylamine ethers incorporating a phosphonate

- 20 group is also illustrated above. In this procedure, a phosphonate 119.4, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 119.5 (Aldrich) to produce the ether 119.6. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine, to give the product 119.6. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 119.7.
- 25



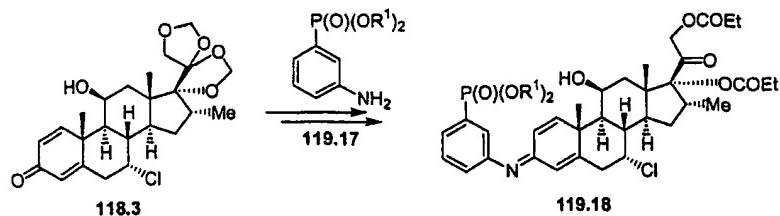
The preparation of phosphonate aclometasone derivatives in which the phosphonate is attached by means of an iminoxy group is shown above. In this procedure, the substrate 118.3 is reacted with a dialkyl phosphonomethyl hydroxylamine 119.8, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (Tet. Lett., 1986, 27, 1477) and BOC-hydroxylamine, to afford, after deprotection and side chain acylation, the oxime ether 119.9. The oxime forming reaction is performed at ambient temperature in pyridine solution between equimolar amounts of the reactants. Using the above procedures, but employing, in place of the oxime ether 119.8, different oxime ethers 119.7, the corresponding products 119.3 are obtained.



The preparation of phosphonate aclometasone derivatives incorporating an iminoxy group, by means of the reaction between the substrate 118.3 and O-2-(3-bromophenyl)ethoxyhydroxylamine 119.10, prepared as described above from 2-(3-bromophenyl)ethyl bromide is illustrated above. The resultant oxime 5 ether is converted, by deprotection and side chain acylation, into the compound 119.11 which is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite 119.12 to afford the phosphonate 119.13. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The reaction is 10 performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

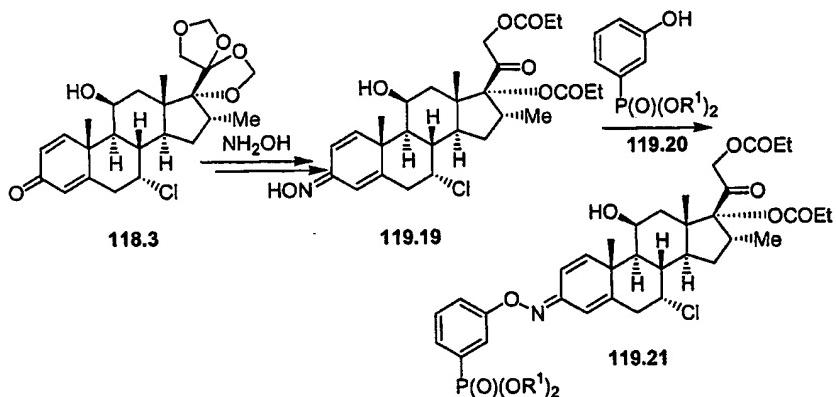
Alternatively, the bromo-substituted product 119.11 is coupled, in a palladium-catalyzed Heck reaction, with a dialkyl vinyl phosphonate 119.14 15 (Aldrich) to give the unsaturated phosphonate 119.15. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the 20 presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 119.15 is reduced, for example by reaction with diimide, 25 to produce the saturated analog 119.16. The reduction of olefinic bonds is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

30 Using the above procedures, but employing, in place of the bromophenyl reagent 119.10, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 119.13, 119.15 and 119.16 are obtained.



The preparation of phosphonate aclometasone derivatives in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate 118.3 is reacted with a dialkyl 3-aminophenyl phosphonate 119.17 (J. Med. Chem., 1984, 27, 654) to give, after deprotection and side chain acylation, the imine product 119.18. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions, to give the product 119.18. Using the above procedures, but employing, in place of the 3-aminophenyl phosphonate 119.17, different amino-substituted aryl or heteroaryl phosphonates, products analogous to 119.18 are obtained.

15

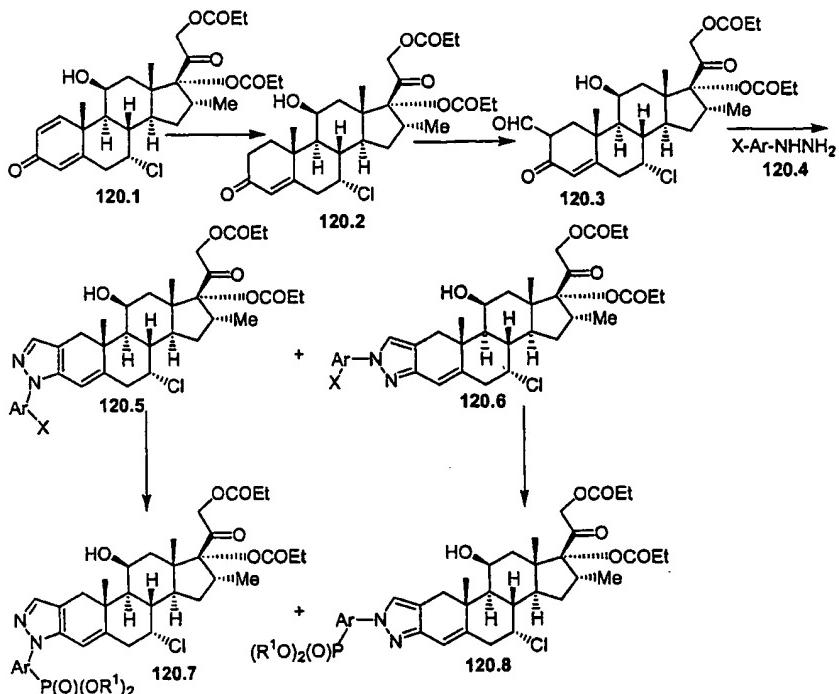


An alternative method for the preparation of phosphonate aclometasone derivatives in which the phosphonate is attached by means of an oximino group is illustrated above. In this procedure, the dienone 118.3 is reacted with hydroxylamine to yield, after deprotection and side chain acylation, the oxime 119.19. The reaction of steroidal 1,4-dien-3-ones with hydroxylamine is

- described in J. Steroid Bioch., 1976, 7, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then reacted with a dialkyl 3-hydroxyphenyl phosphonate **119.20** (Epsilon) in
- 5 a Mitsonobu reaction, to yield the substituted oxime **119.21**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335.
- 10 The phenol and the hydroxy or mercapto component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656.

Using the above procedures, but employing, in place of the phosphonate
15 **119.20**, different dialkyl hydroxy-substituted aryl or heteroaryl phosphonates, the products analogous to **119.21** are obtained.

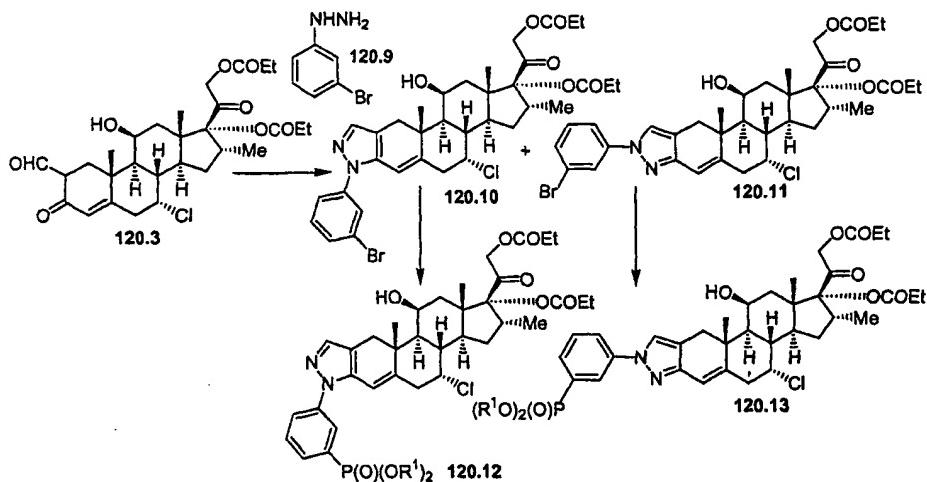
Example 120 Preparation of Representative Aclometasone Derivatives



The preparation of the phosphonate aclometasone derivatives in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by 5 means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, Aclometasone dipropionate 120.1 is reduced to afford the 1,2-dihydro product, 120.2. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in J. Med. Chem., 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in 10 Australian Patent Application 275950409, to afford the 2-formyl product 120.3. Optionally, the substrate 120.1 is protected prior to the formylation reaction, as 15 described in J. Am. Chem. Soc., 1964, 86, 1520. The 2-formyl product is then reacted with an aryl or heteroaryl hydrazine 120.4, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles 120.5 and 120.6. The ring-forming reaction is

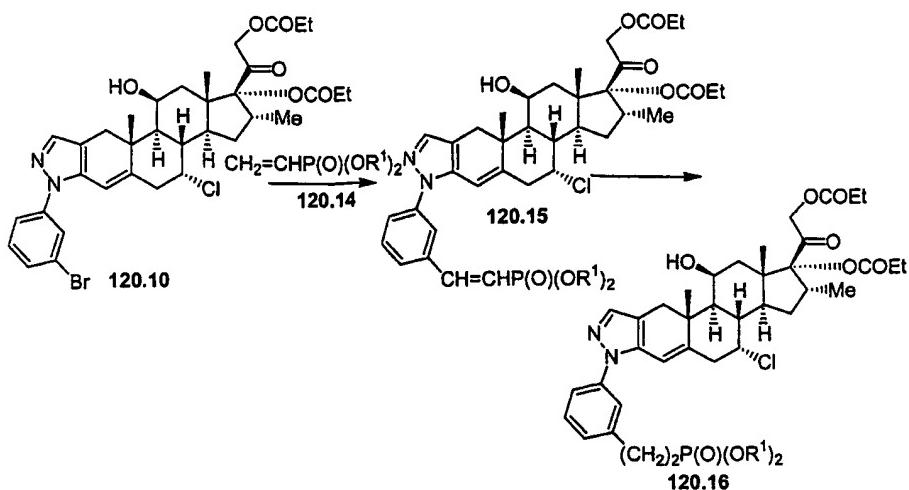
performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in J. Am. Chem. Soc., 1964, 86, 1520. The pyrazoles **120.5** and **120.6** are then transformed, respectively, into the phosphonates **120.7** and **120.8**.

5



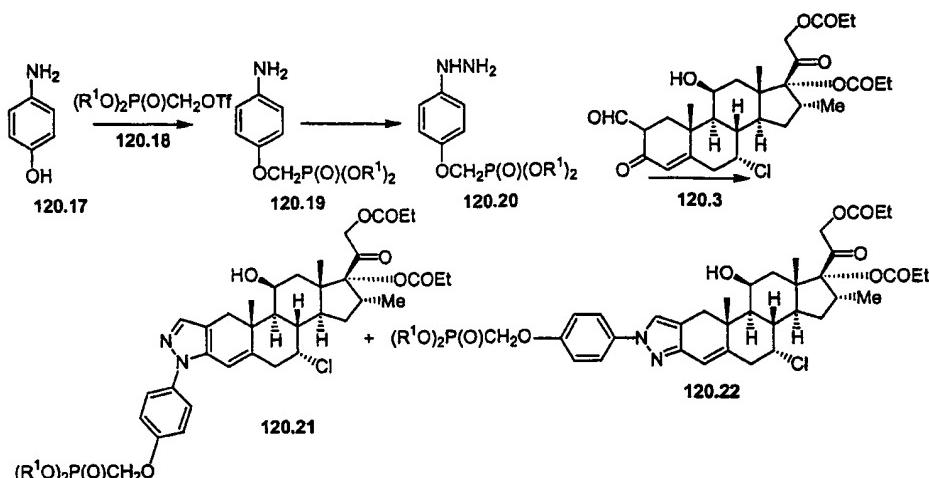
The preparation of phosphonate aclometasone derivatives in which the phosphonate is attached by means of a phenyl group is illustrated above. In this sequence, the ketoaldehyde **120.3** is reacted, as described above, with 3-bromophenylhydrazine **120.9** (Fluka), to give the isomeric pyrazole products **120.10** and **120.11**. The products are then reacted, as described above, with a dialkyl phosphite HP(O)(OR')_2 and a palladium catalyst, to afford respectively the phosphonates **120.12** and **120.13**.

Using the above procedures, but employing, in place of 3-bromophenyl hydrazine, different bromoaryl or bromoheteroaryl hydrazines **12.4**, the corresponding products **120.7** and **120.8** are obtained.



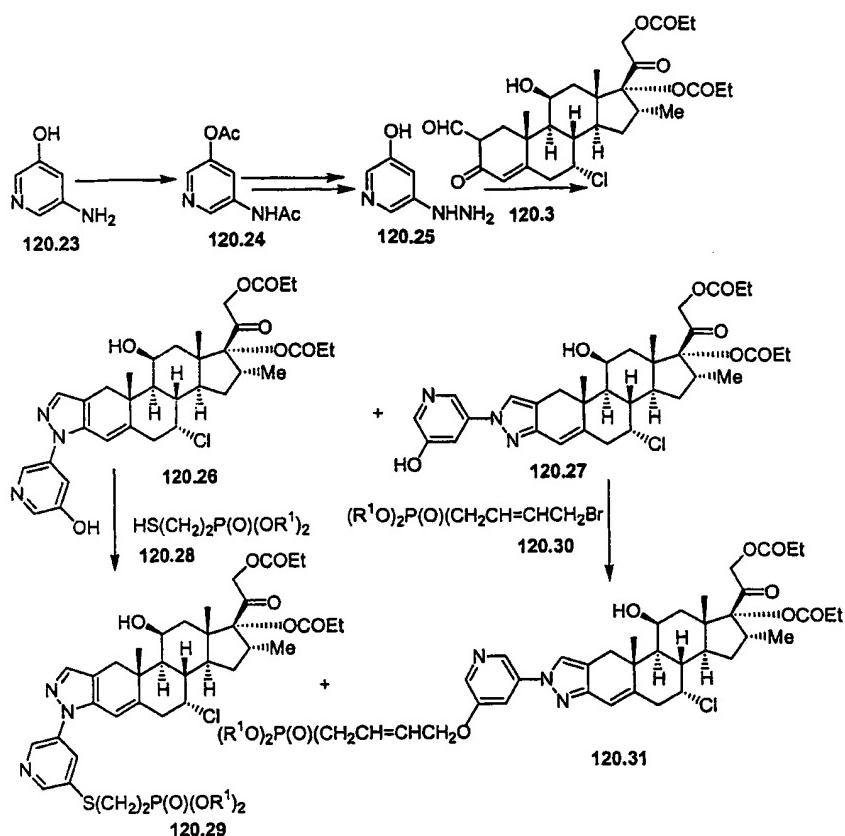
The preparation of phosphonate aclometasone derivatives in which the phosphonate is attached by means of an aromatic or heteroaromatic group and a
 5 saturated or unsaturated alkyl chain is illustrated above. In this procedure, the bromophenyl-substituted pyrazole 120.10 is coupled in a Heck reaction, as
 described above, with, for example a dialkyl vinyl phosphonate 120.14 (Aldrich)
 to give the unsaturated phosphonate product 120.15. Optionally, the product is
 reduced, as described above, to give the saturated analog 120.16. Application of
 10 the above procedures to the isomeric bromophenyl pyrazole 120.11 affords the
 products isomeric with 120.15 and 120.16.

Using the above procedures, but employing, in place of the phosphonate
 120.14, different dialkyl alkenyl phosphonates, and/or different bromoaryl or
 heteroaryl pyrazoles 120.5 or 120.6 (X = Br) the products analogous to 120.15
 15 and 120.16 are obtained.



The preparation of phosphonate aclometasone derivatives in which the phosphonate is attached by means of an aryl or heteroaryl group and an alkoxy chain is illustrated above. In this procedure, 4-aminophenol **120.17** is reacted in dimethylformamide solution at ambient temperature with a dialkyl trifluoromethanesulfonyloxyethyl phosphonate **120.18** (Tet. Lett., 1986, 27, 1477) and potassium carbonate to give the ether **120.19**. The product is then converted into the corresponding hydrazine **120.20** by means of a diazotization reaction in aqueous ethanolic hydrochloric acid, followed by reduction of the diazonium chloride with tin(II) chloride, as described in J. Med. Chem., 2001, 44, 4031. The hydrazine is then reacted, as described above, with the ketoaldehyde **120.3**, to form the isomeric pyrazoles **120.21** and **120.22**.

Using the above procedures, but employing, in place of the triflate **120.18**, different dialkylphosphono alkyl bromides or triflates, and/or different aromatic or heteroaromatic hydroxyamines, the products analogous to **120.21** and **120.22** are obtained.



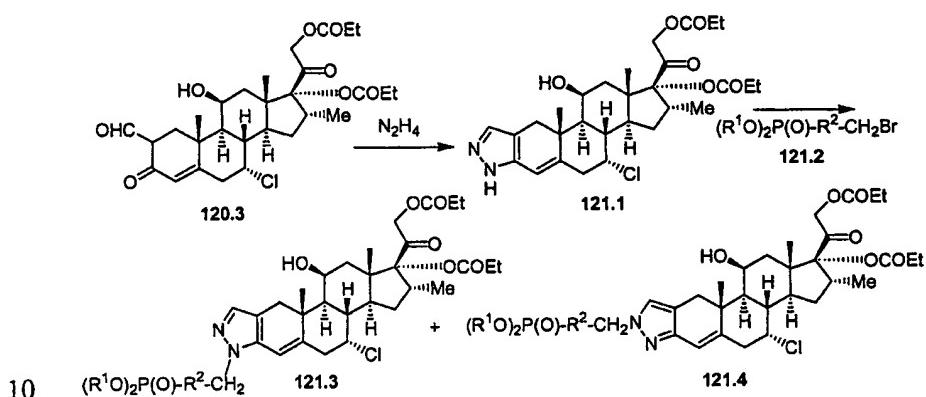
The preparation of phosphonate aclometasone derivatives in which the phosphonate is attached by means of a pyridyl group a heteroatom and a variable carbon chain is illustrated above. In this procedure, 3-amino-5-hydroxypyridine is converted, by reaction with acetic anhydride, into the diacetyl analog 120.24. The product is then transformed by diazotization and reduction, as described above, into the hydrazine 120.25. The hydrazine is then reacted with the 2'-pyridyl product 120.26 is reacted in a Mitsonobu reaction, as described above, with a dialkyl mercaptoethyl phosphonate 120.28 (Zh. Obschei. Khim., 1973, 43, 2364) to afford the thioether 120.29. Application of this procedure to the isomeric phenol 120.27 affords the product isomeric to 120.29.

Alternatively, the isomeric phenol 120.27 is reacted, in dimethylformamide solution at ca. 80°, with one molar equivalent of a dialkyl bromobut enyl phosphonate 120.30 (J. Med. Chem., 1992, 35, 1371) and cesium

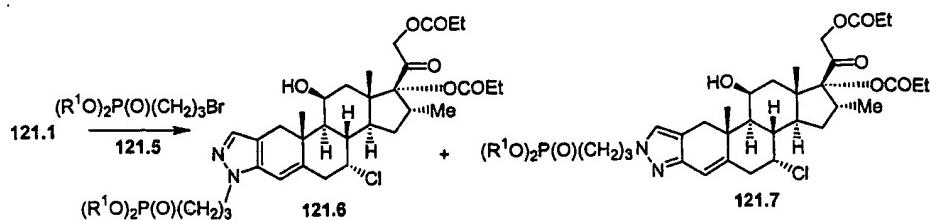
carbonate, to prepare the phosphonate **120.31**. Application of this procedure to the isomeric phenol **120.26** affords the product isomeric with **120.31**.

Using the above procedures, but employing, in place of the thiol 120.28 or the bromide 120.30, different thiols, alcohols or bromides, and/or different phenols 120.5 or 120.6 in which X is OH, the corresponding products analogous to 120.29 and 120.31 are obtained.

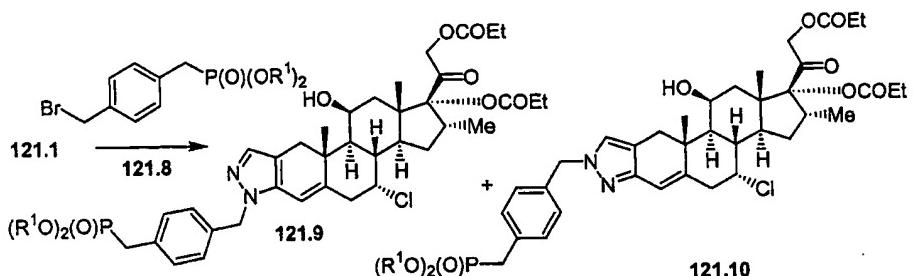
Example 121 Preparation of Representative Aclometasone Derivatives



The preparation of representative compounds of the invention in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde 120.3 is reacted with 15 hydrazine, to afford the pyrazole derivative 121.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in J. Am. Chem. Soc, 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The resulting pyrazole is then reacted with a dialkyl bromomethyl phosphonate 121.2, in which R² is as defined above, to produce the isomeric 2' and 1' 20 alkylation products 121.3 and 121.4 respectively. The alkylation of substituted pyrazoles is described, for example, in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 309.



The preparation of representative compounds of the invention is illustrated above. The pyrazole 121.1 is reacted, in dimethylformamide solution at ca. 90°, with a dialkyl bromopropyl phosphonate 121.5 (Aldrich) and a base such as dimethylaminopyridine or lithium hexamethyldisilazide, to yield the isomeric alkylation products 121.6 and 121.7.



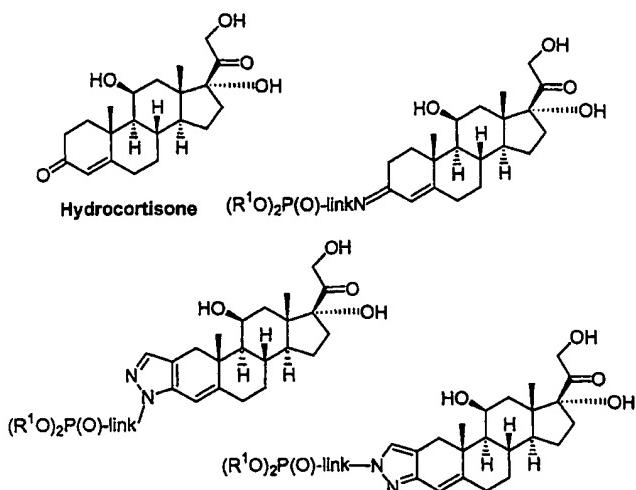
10

The preparation of representative compounds of the invention is illustrated above. The pyrazole 121.1 is reacted, as described above, with a dialkyl 4-bromomethyl benzyl phosphonate 121.8 (Tet. 1998, 54, 9341) to give the products 121.9 and 121.10.

15

Examples 122-125 – Hydrocortisone Derivatives

The structures of hydrocortisone and representative phosphonate esters of the invention are shown below, in which the substituent R¹ is H, alkyl, alkenyl, aryl or aralkyl. These compounds incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.

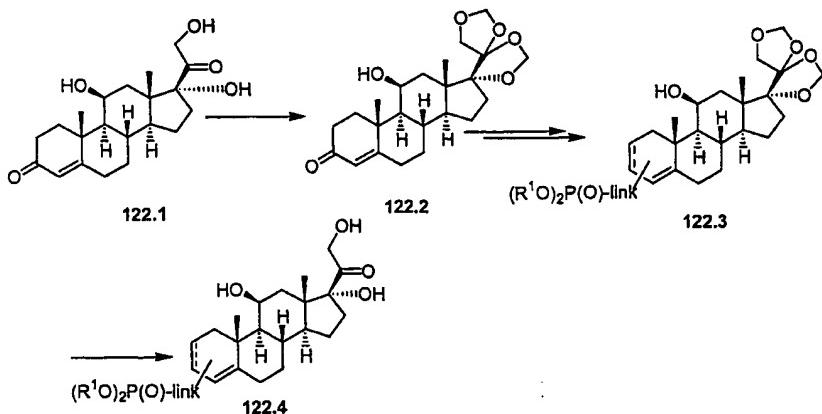


The synthesis of representative phosphonate derivatives of hydrocortisone is

outlined in Examples 122-125. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection

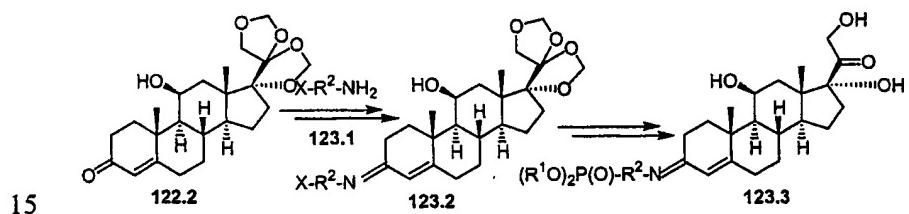
- 5 before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in
- 10 Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

15 Example 122 Preparation of Representative Hydrocortisone Derivatives



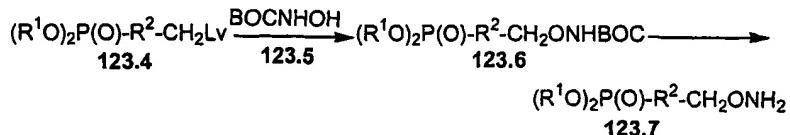
As illustrated above, the steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, hydrocortisone **122.1** is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative **122.2**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester **122.3**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol **122.4**

Example 123 Preparation of Representative Hydrocortisone Derivatives

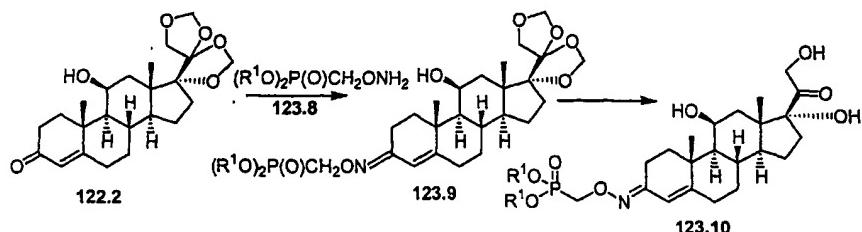


The preparation of hydrocortisone phosphonate derivatives in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative **122.2** is reacted with an amine or hydroxylamine **123.1**, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of

an acid catalyst, to give the imine or oxime 123.2. The preparation of oximes of steroidal 3-ketones is described in Anal. Bioch., 1978, 86, 133. and in J. Mass. Spectrom., 1995, 30, 497. In cases in which X is not dialkylphosphono, the substituent X is converted, using the methods described below; into a 5 phosphonate-containing substituent; the BMD-protected side-chain is then removed to afford the triol 123.3.



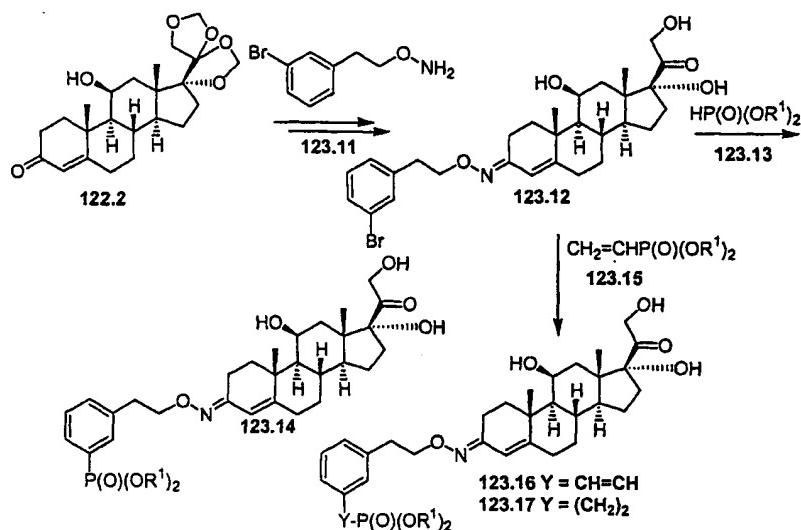
10 The preparation of intermediate hydroxylamine ethers incorporating a phosphonate group is illustrated above. In this procedure, a phosphonate 123.4, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 123.5 (Aldrich) to produce the ether 123.6. The reaction is conducted between equimolar amounts of the reactants in a polar 15 solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 123.7.



20

The preparation of hydrocortisone phosphonate derivatives in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate 122.2 is reacted with a dialkyl phosphonomethyl 25 hydroxylamine 123.8, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (Tet. Lett., 1986, 27, 1477) and BOC-hydroxylamine, to afford the oxime 123.9 which is deprotected to afford

the triol 123.10. The oxime forming reaction is typically performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants. Using the above procedures, but employing, in place of the hydroxylamine ether 123.8, different oxime ethers 123.7, the corresponding products 123.3 are obtained.

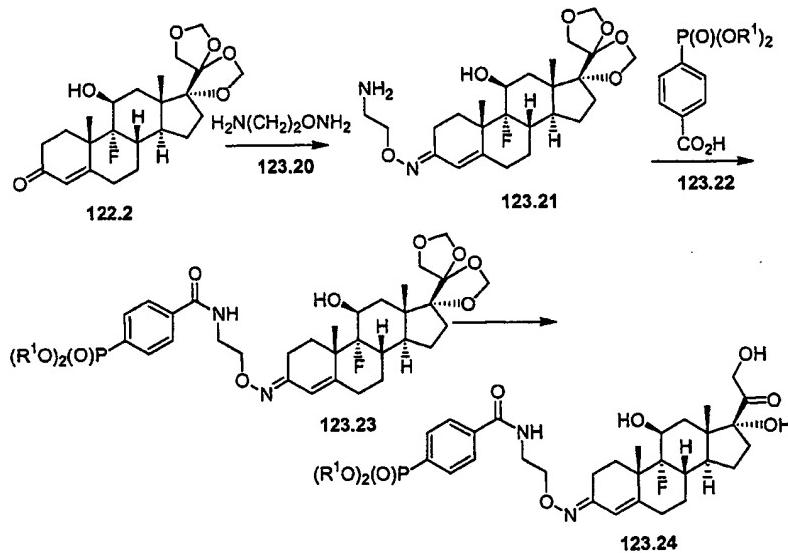


The preparation of hydrocortisone phosphonate derivatives in which the phosphonate group is attached by means of a phenyl ethoxy group is illustrated above. In this procedure, the enone 122.2 is reacted, as described above, with O-(3-bromophenyl)ethyl hydroxylamine 123.11, prepared as described above from 2-(3-bromophenyl)ethyl bromide (French Patent FR 1481052), to give, after deprotection of the side-chain, the oxime 123.12. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite 123.13 to afford the phosphonate 123.14. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound 123.12 is coupled with a dialkyl vinylphosphonate 123.15 (Aldrich) to afford the phosphonate 123.16. The coupling of aryl halides with olefins by means of the Heck reaction is described,

for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as 5 tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 123.16 is reduced, for example by reaction with diimide, to produce the saturated analog 123.17. The reduction of olefinic bonds is 10 described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromophenyl 15 ethoxy reagent 123.11, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 123.14, 123.16 and 123.17 are obtained.



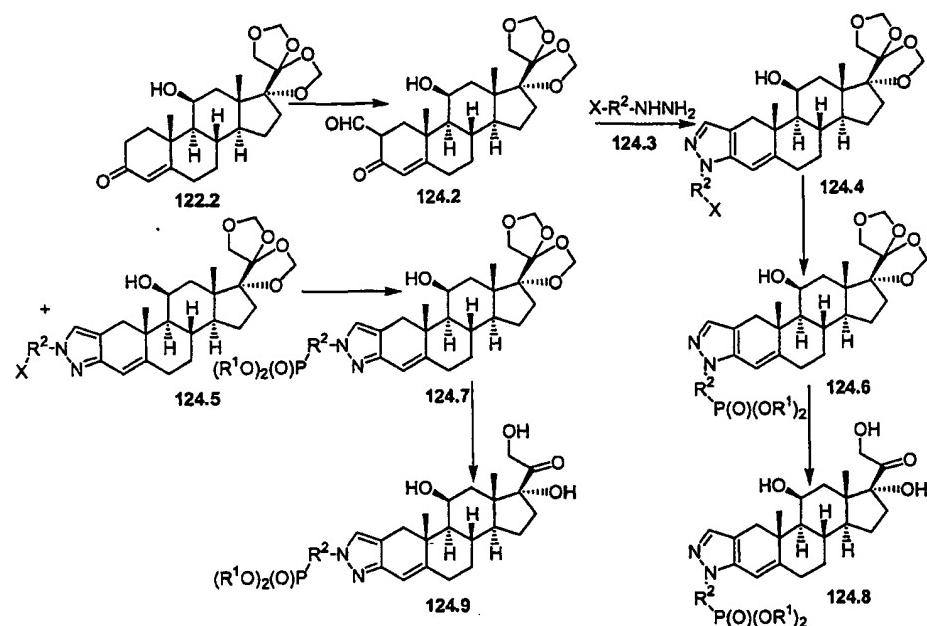
20

The preparation of hydrocortisone phosphonate derivatives in which the phosphonate is attached by means of an oximino group and an amide linkage is

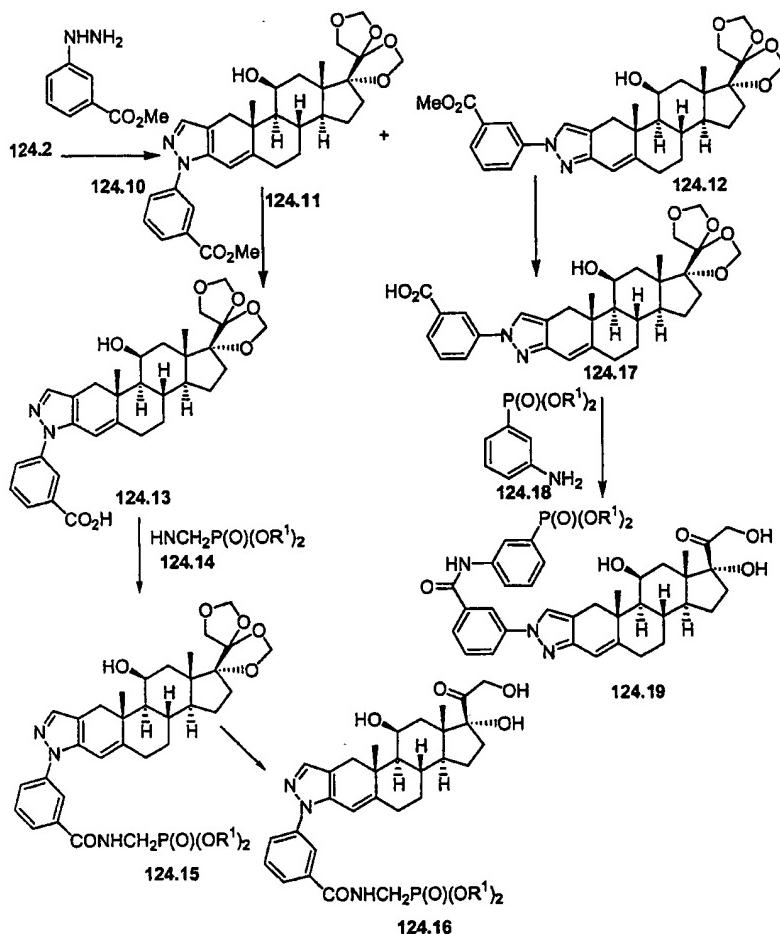
illustrated above. In this procedure, the enone 122.2 is reacted with O-(2-aminoethyl)hydroxylamine 123.20 (Pol. J. Chem., 1981, 55, 1163) to yield the oxime 123.21. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in J. Steroid Bioch., 1976, 7, 795. The reaction is 5 performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then coupled with a dialkyl 4-carboxyphenyl phosphonate 123.22 (Epsilon), to yield the amide oxime 123.23. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic 10 Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, 15 hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide 20 and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in 25 the presence of a catalytic amount of dimethylformamide. The amide product 123.23 is then converted into the triol 123.24. Using the above procedures, but employing, in place of the hydroxylamine 123.20, different amino-substituted hydroxylamines, and/or different carboxy-substituted phosphonates, the products analogous to 123.24 are obtained.

Example 124 Preparation of Representative Hydrocortisone Derivatives



5 The preparation of hydrocortisone phosphonate derivatives in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of a variable carbon chain is illustrated above. In this procedure, the BMD-protected enone 124.1 is reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, 1964, 86, 1520, to afford the 2-formyl product 124.2. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine 124.3, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, 10 carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles 124.4 and 124.5. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The pyrazoles 124.4 and 124.5 are then 15 transformed via the BMD-protected intermediates 124.6 and 124.7, into the phosphonates 124.8 and 124.9.

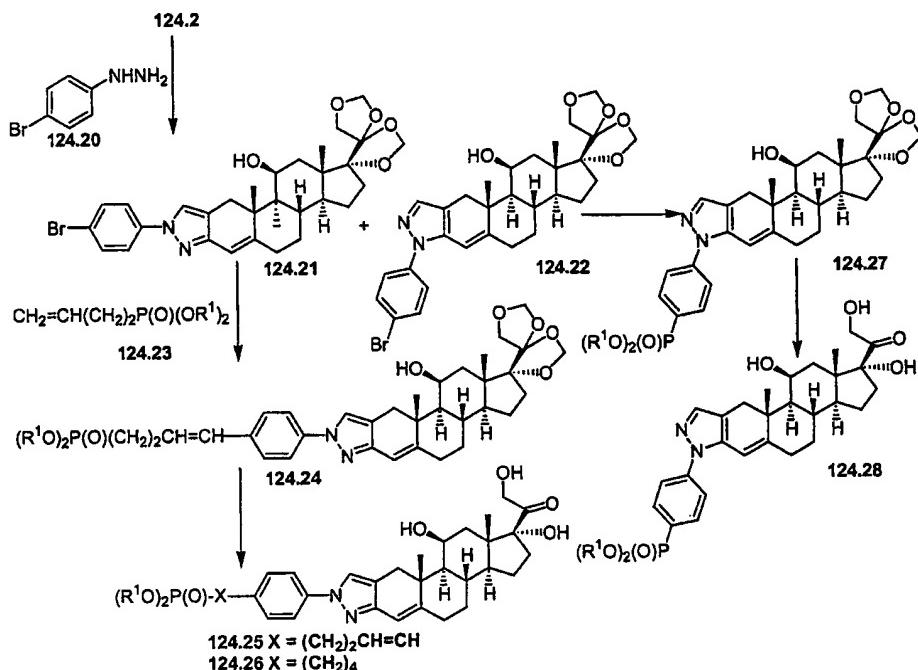


The preparation of hydrocortisone phosphonate derivatives in which the phosphonate moiety is attached by means of a phenyl ring and an amide linkage

- 5 is illustrated above. In this procedure, the ketoaldehyde 124.2 is reacted, as described above, with 3-carbomethoxyphenylhydrazine 124.10 (Apin) to give the pyrazoles 124.11 and 124.12. The 2'-substituted isomer 124.11 is then reacted with one molar equivalent of lithium hydroxide in aqueous dimethoxyethane, to produce the carboxylic acid 124.13. The acid is then 10 coupled, as described above, with a dialkyl aminomethyl phosphonate 124.14 (Interchim) to give the amide 124.15; deprotection then affords the triol 124.16.

Alternatively, the 1'-substituted pyrazole 124.12 is hydrolyzed, as described above, to the carboxylic acid 124.17. The product is then coupled with a dialkyl 3-aminophenyl phosphonate 124.18 (J. Med. Chem., 1984, 27, 654) to

yield after deprotection the triol amide 124.19. Using the above procedures, but employing, in place of the carbomethoxyphenyl hydrazine 124.20, different carbomethoxy-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl amino-substituted phosphonates, the products analogous to the compounds 124.16 and 124.19 are obtained.



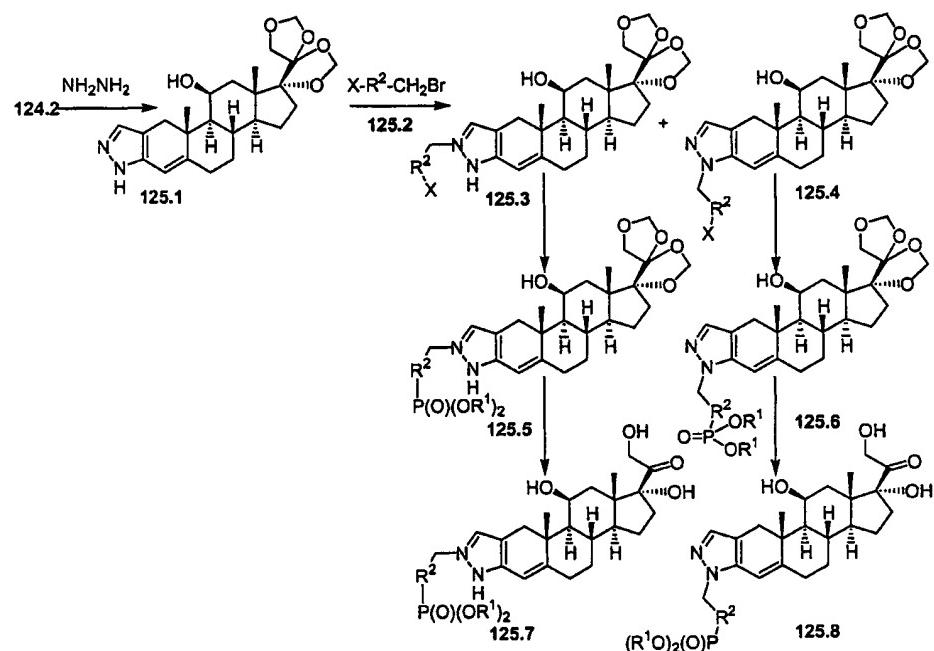
The preparation of hydrocortisone phosphonate derivatives in which the phosphonate group is attached by means of a phenyl group or a phenyl group and a saturated or unsaturated carbon chain is illustrated above. In this procedure, the ketoaldehyde 124.2 is reacted, as described above, with 4-bromophenyl hydrazine 124.20 (*J. Organomet. Chem.*, 1999, 62, 581) to produce the pyrazoles 124.21 and 124.22. The 1'-substituted isomer 124.21 is coupled, as described above, in the presence of a palladium catalyst, with a dialkyl butenyl phosphonate 124.23 (*Org. Lett.*, 2001, 3, 217) to give the phosphonate 124.24. The product is then deprotected to afford the triol 124.25. Optionally, the styrenoid double bond present in the product 124.25 is reduced, as described above, to produce the saturated analog 124.26.

Alternatively, the 2'-substituted pyrazole 124.22 is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite to prepare the

phosphonate 124.27 which is deprotected to give the triol 124.28. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and tetrakis(triphenylphosphine)-palladium(0). Using the above procedures, but employing, in place of the bromophenyl hydrazine 124.20, different bromo-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 124.25, 124.26 and 124.28 are obtained.

10

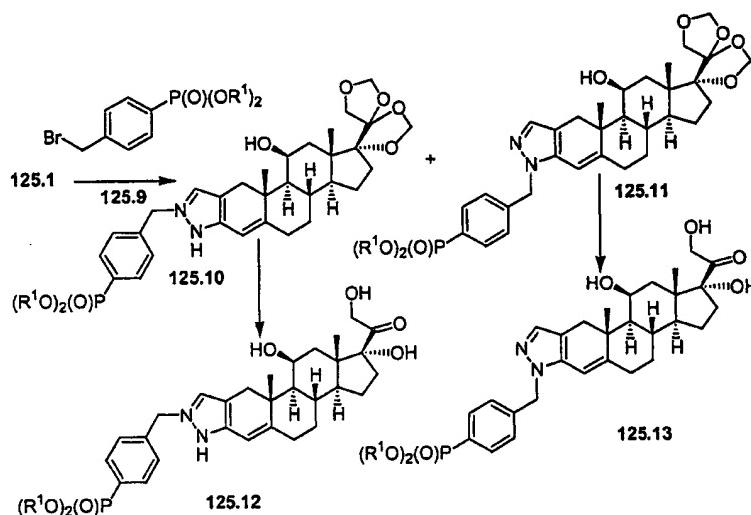
Example 125 Preparation of Representative Hydrocortisone Derivatives



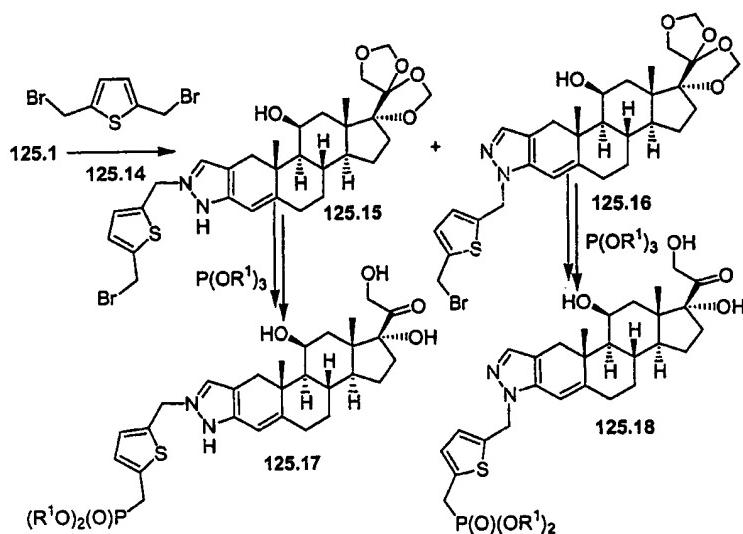
The preparation of hydrocortisone phosphonate derivatives in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde 124.2 is reacted with hydrazine, to afford the pyrazole derivative 125.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The reaction is performed in ethanol at reflux temperature. The pyrazole product is then reacted with a bromomethyl compound 125.2, in which R² and X

are as defined above, to yield the alkylation products **125.3** and **125.4**. The alkylation of substituted pyrazoles is described, for example, in *Heterocyclic Chemistry*, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as
 5 dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products **125.3** and **125.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates **125.5** and **125.6**, using the procedures described herein, and deprotection then affords the triols **125.7** and **125.8**.

10



Representative hydrocortisone derivatives can be prepared as illustrated above. The pyrazole **125.1** is reacted, as described above, with one molar
 15 equivalent of a dialkyl 4-(bromomethyl)phenyl phosphonate **125.9** (WO 2003042150) to give the alkylated pyrazoles **125.10** and **125.11**. Deprotection then yields the triols **125.12** and **125.13**.



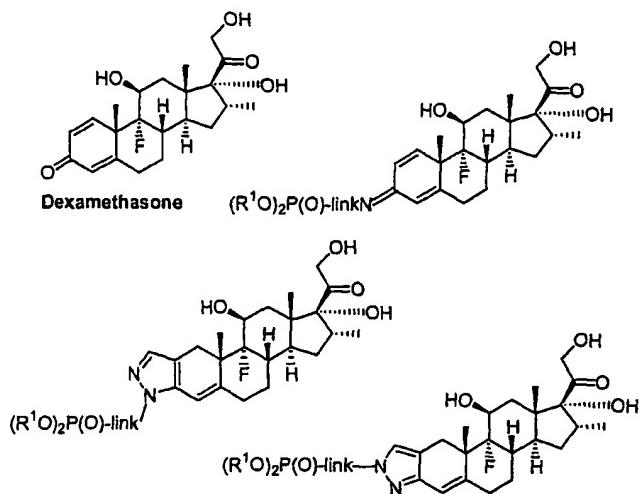
Representative hydrocortisone derivatives can be prepared as illustrated above. The pyrazole 125.1 is reacted, as described above, with 2,5-

- 5 bis(bromomethyl)thiophene 125.14 (*Tet.* 1999, 55, 4709) to give the pyrazoles 125.15 and 125.16. The products are subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain, the phosphonates 125.17 and 125.18. The 10 Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, 1992, 115-72. In the procedure, the substrate is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite.

Using the above procedures, but employing, in place of the dibromide 125.14, different dibromides, the products analogous to 125.17 and 125.18 are 15 obtained.

Examples 126-129 – Dexamethasone Derivatives

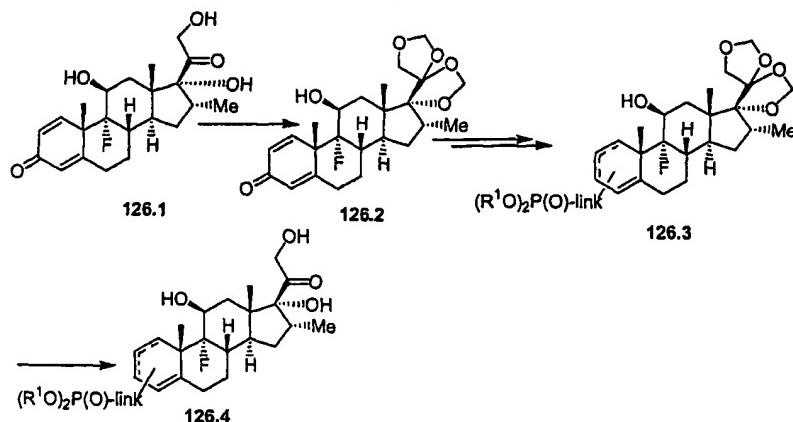
The structures of dexamethasone and representative phosphonate esters of the invention are shown below, in which the substituent R¹ is H, alkyl, 20 alkenyl, aryl or aralkyl. These compounds incorporate a phosphonate moiety (R'¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.



The synthesis of representative phosphonate derivatives of hydrocortisone is

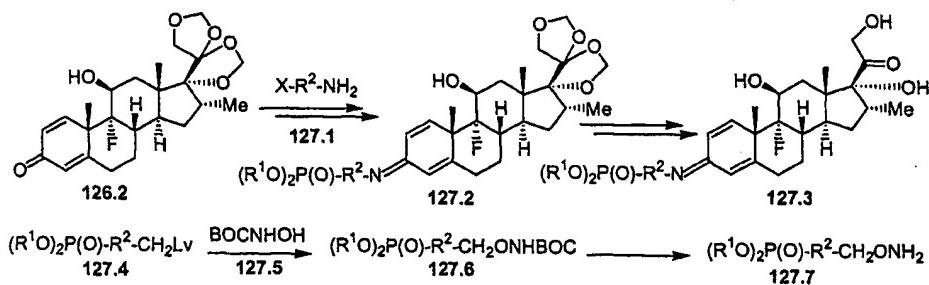
outlined in Examples 126-129. In these Examples, it may be necessary to

- 5 protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The
- 10 protection and deprotection of steroidal ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 126 Preparation of Representative Dexamethasone Derivatives

The steroid side-chain is protected as a bis-methylenedioxy (BMD)

- 5 moiety. In this sequence, Dexamethasone 126.1 is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative 126.2. The phosphonate moiety is then introduced, using the procedures described below, to
10 produce the phosphonate ester 126.3. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol 126.4

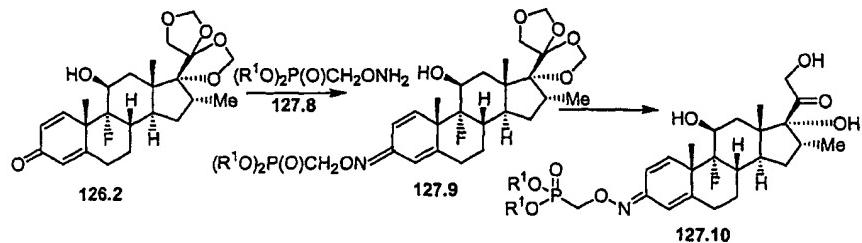
15 Example 127 Preparation of Representative Dexamethasone Derivatives

The preparation of dexamethasone phosphonates in which the

- phosphonate is attached by means of an imino or iminooxy group and a variable
20 carbon chain is illustrated above. In this procedure, the BMD-protected

derivative 126.2 is reacted with an amine or hydroxylamine 127.1, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in Anal. Bioch., 1978, 86, 133. and in J. Mass. Spectrom., 1995, 30, 497. The BMD-protected side-chain compound 127.2 is then converted into the triol 127.3.

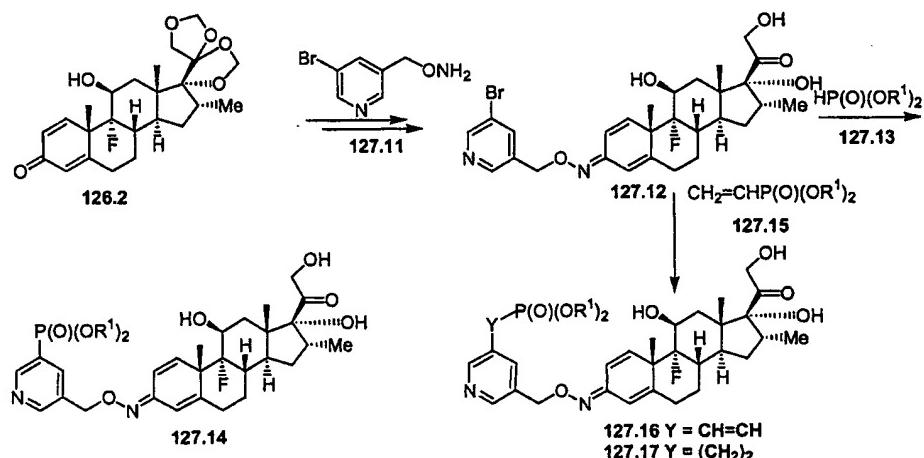
The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate 127.4, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 127.5 (Aldrich) to produce the ether 127.6. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 127.7.



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The preparation of dexamethasone phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate 126.2 is reacted with a dialkyl phosphonomethyl

hydroxylamine **127.8**, prepared as described above from a dialkyl trifluoromethylsulfonyloxyethyl phosphonate (*Tet. Lett.*, 1986, 27, 1477) and BOC-hydroxylamine, to afford the oxime **127.9** which is deprotected to afford the triol **127.10**. The oxime forming reaction is performed at ambient 5 temperature in ethanol-acetic acid solution between equimolar amounts of the reactants. Using the above procedures, but employing, in place of the hydroxylamine ether **127.8**, different oxime ethers **127.1**, the corresponding products **127.3** are obtained.

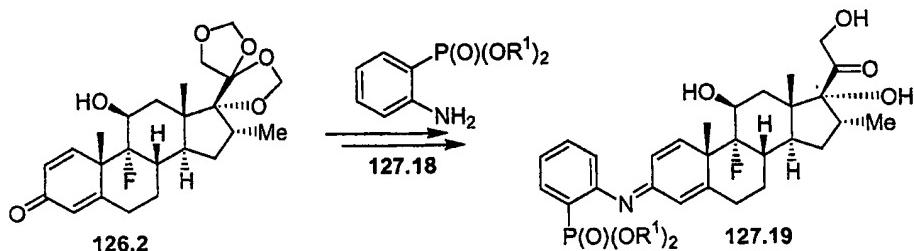


The preparation of dexamethasone compounds in which the phosphonate group is attached by means of a pyridyl methoxy group is illustrated above. In this procedure, the dienone **126.2** is reacted, as described above, with O-(3-bromo-5-pyridylmethyl)hydroxylamine **127.11**, prepared as described above 15 from 3-bromo-5-bromomethylpyridine (WO 9528400), to give, after deprotection of the side-chain, the oxime **127.12**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **127.13** to afford the phosphonate **127.14**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The reaction is performed in an inert solvent 20 such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound 127.12 is coupled with a dialkyl vinylphosphonate 127.15 (Aldrich) to afford the phosphonate 127.16. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J.

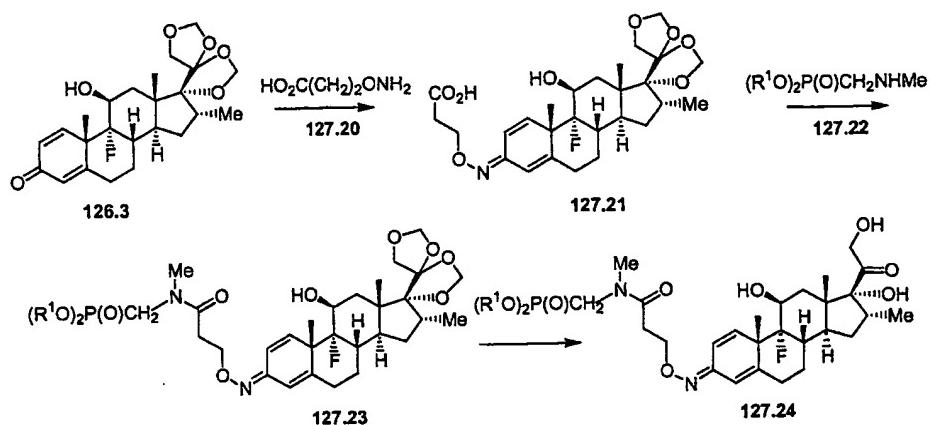
- 5 Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The
aryl bromide and the olefin are coupled in a polar solvent such as
dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as
palladium(II) acetate, and optionally in the presence of a base such as
10 triethylamine or potassium carbonate. Optionally, the styrenoid double bond
present in the product 127.16 is reduced, for example by reaction with diimide,
to produce the saturated analog 127.17. The reduction of olefinic bonds is
described in Comprehensive Organic Transformations, by R. C. Larock, VCH,
1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation,
15 for example using a palladium on carbon catalyst and hydrogen or a hydrogen
donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromopyridyloxy reagent 127.11, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 127.14, 127.16 and 127.17 are obtained.



- The preparation of dexamethasone phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate **126.2** is reacted with a dialkyl 2-aminophenyl phosphonate **127.18**, (*Syn.*, 1999, 1368) to give, after deprotection, the imine product **127.19**. The reaction is conducted in a hydrocarbon solvent such as

toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. Using the above procedures, but employing, in place of the 2-aminophenyl phosphonate 127.18 different amino-substituted aryl or
5 heteroaryl phosphonates, products analogous to 127.19 are obtained.



The preparation of dexamethasone phosphonates in which the phosphonate is attached by means of an oximino group and an amide linkage is illustrated above. In this procedure, the dienone 126.2 is reacted with O-(2-carboxyethyl)hydroxylamine 127.20 (*J. Med. Chem.*, 1990, 33, 1423) to yield the oxime 127.21. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, 1976, 7, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then reacted with a dialkyl aminomethyl phosphonate 127.22 (AsInEx), to yield the amide oxime 127.23. The preparation of amides from carboxylic acids and derivatives is described, for example, in *Organic Functional Group Preparations*, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, 20 hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-
25

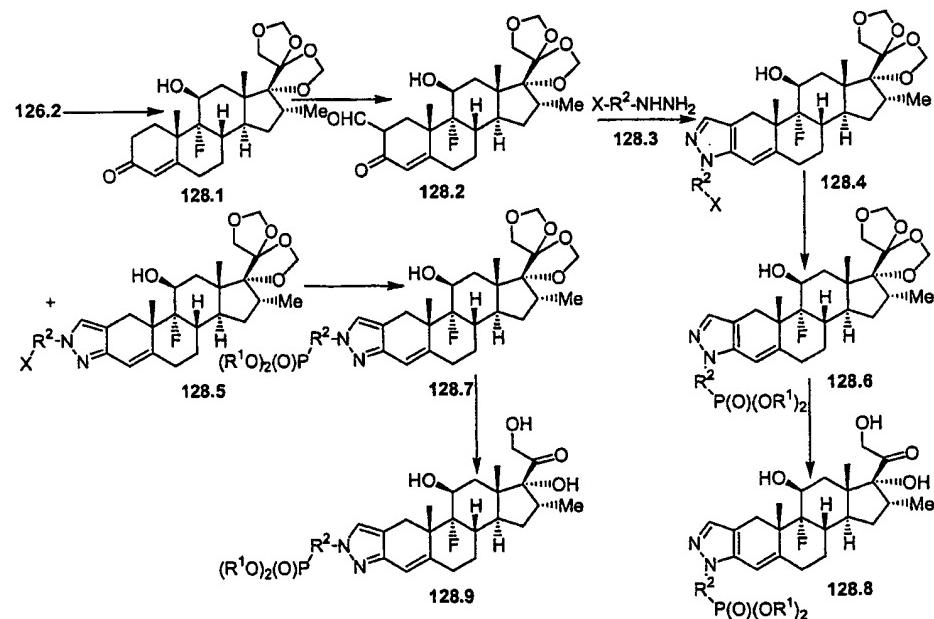
protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

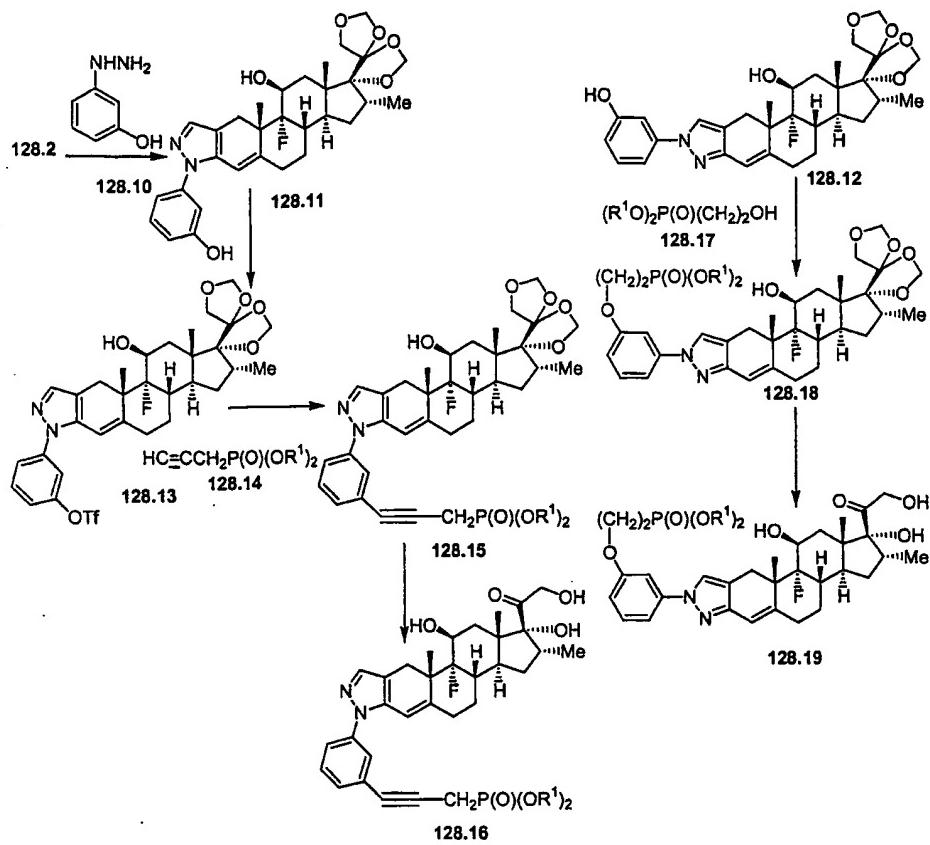
The amide product 127.23 is then converted into the triol 127.24.

Using the above procedures, but employing, in place of the hydroxylamine 127.22, different carboxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to 127.24 are obtained.

Example 128 Preparation of Representative Dexamethasone Derivatives

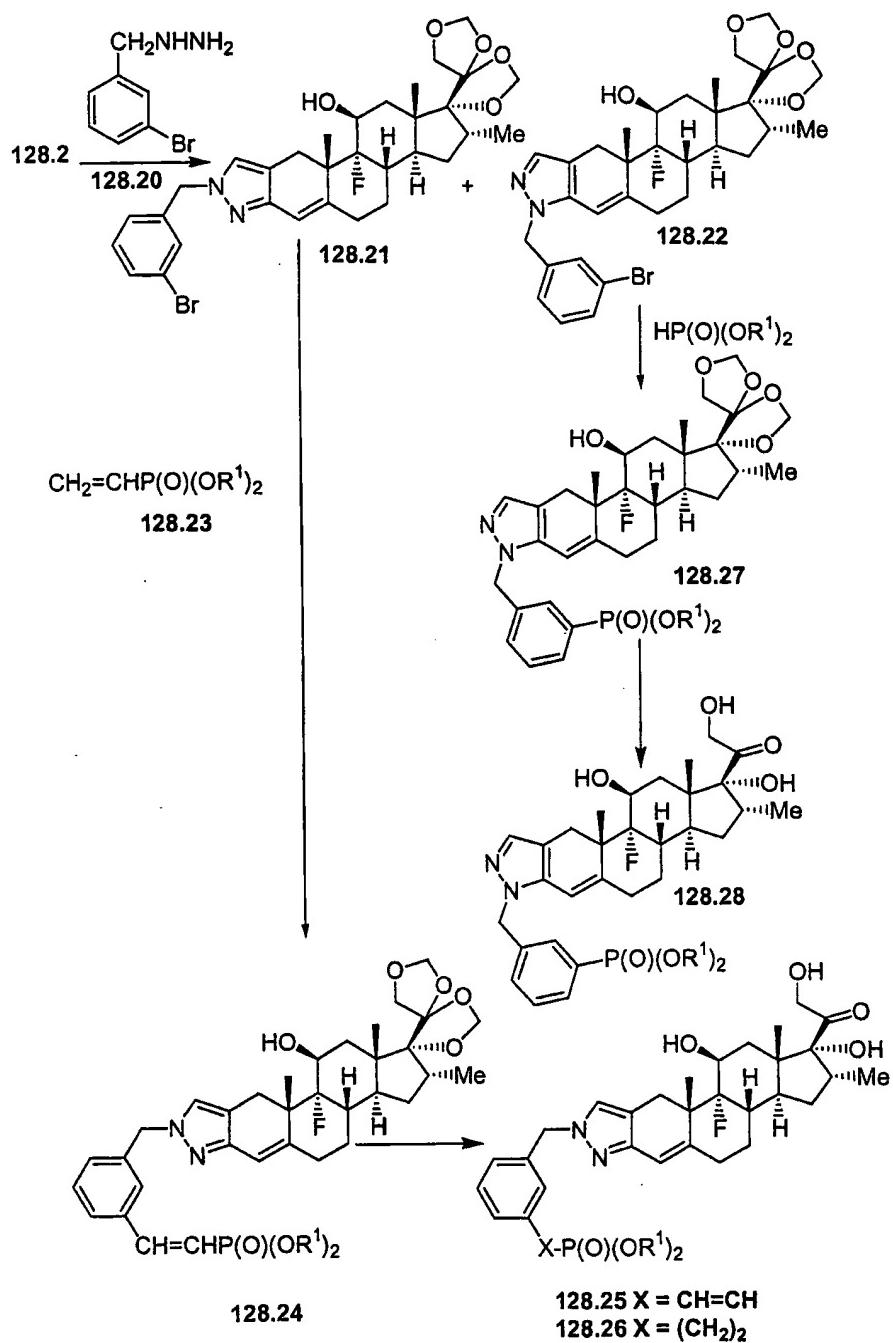


The preparation of the dexamethasone phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, the BMD-protected dienone 5 **126.2** is reduced to afford the 1,2-dihydro product **128.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in J. Med. Chem., 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in J. Am. 10 Chem. Soc., 1964, 86, 1520, to afford the 2-formyl product **128.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine **128.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. 15 The reaction yields the isomeric 2'- and 1'-aryl pyrazoles **128.4** and **128.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in J. Am. Chem. Soc., 1964, 86, 1520. The pyrazoles **128.4** and **128.5** are then transformed via the BMD-protected intermediates **128.6** and **128.7**, into the phosphonates **128.8** 20 and **128.9**.



The preparation of dexamethasone phosphonates in which the phosphonate is attached by means of a phenyl ring and an alkoxy or an acetylenic linkage is illustrated above. In this procedure, the ketoaldehyde 128.2 is reacted with 3-hydroxyphenylhydrazine 128.10 (Japanese patent JP 03011081) to give the pyrazoles 128.11 and 128.12. The 2'-substituted isomer 128.11 is then reacted in dichloromethane solution at ambient temperature with one molar equivalent of trifluoromethylsulfonyl chloride and 5 dimethylaminopyridine, to yield the triflate 128.13. The product is then reacted in toluene solution with a dialkyl propynyl phosphonate 128.14 (*Syn* 1999, 2027), triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium (0), to give the acetylenic product 128.15. The palladium-catalyzed coupling reaction of aryl triflates with terminal 10 acetylenes is described in WO 0230930. The BMD protecting group is then removed to yield the triol 128.16.

Alternatively, the 1'-substituted pyrazole **128.12** is reacted, in a Mitsonobu reaction, with a dialkyl 2-hydroxyethyl phosphonate **128.17** (Epsilon) to afford the ether **128.18**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, 1992, 42, 335-656. The product **128.18** is then deprotected to give the triol **128.19**. Using the above procedures, but employing different acetylenic or hydroxyl-substituted phosphonates, the products analogous to **128.16** and **128.19** are obtained. The functionalization procedures are interchangeable between the pyrazole substrates **128.11** and **128.12**.

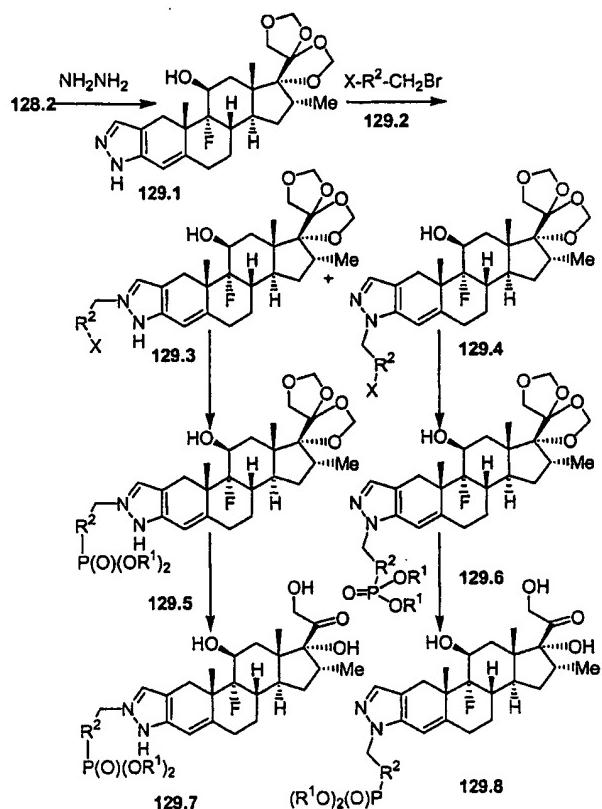


The preparation of dexamethasone phosphonates in which the phosphonate group is attached by means of a benzyl group or a benzyl group and a saturated or unsaturated carbon chain is illustrated above. In this procedure, the 5 ketoaldehyde 128.2 is reacted, as described above, with 3-bromobenzyl hydrazine 128.20 (US Patent 4370339) to produce the pyrazoles 128.21 and

128.22. The 1'-substituted isomer 128.21 is coupled, in the presence of a palladium catalyst, with a dialkyl vinylphosphonate 128.23(Aldrich) to give the phosphonate 128.24. The product is then deprotected to afford the triol 128.25. Optionally, the styrenoid double bond present in the product 128.25 is reduced,
5 as described above, to produce the saturated analog 128.26.

Alternatively, the 2'-substituted pyrazole 128.22 is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite to prepare the phosphonate 128.27 which is deprotected to give the triol 128.28. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.
10 This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and tetrakis(triphenylphosphine)-palladium(0).

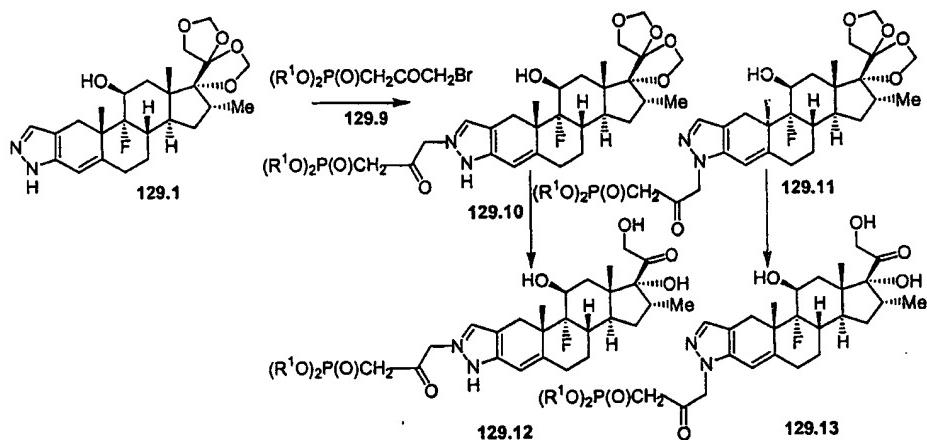
Using the above procedures, but employing, in place of the bromobenzyl reagent 128.20, different bromo-substituted aralkyl, aryl or heteroaryl alkoxy
15 hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 128.25, 128.26 and 128.28 are obtained.

Example 129 Preparation of Representative Dexamethasone Derivatives

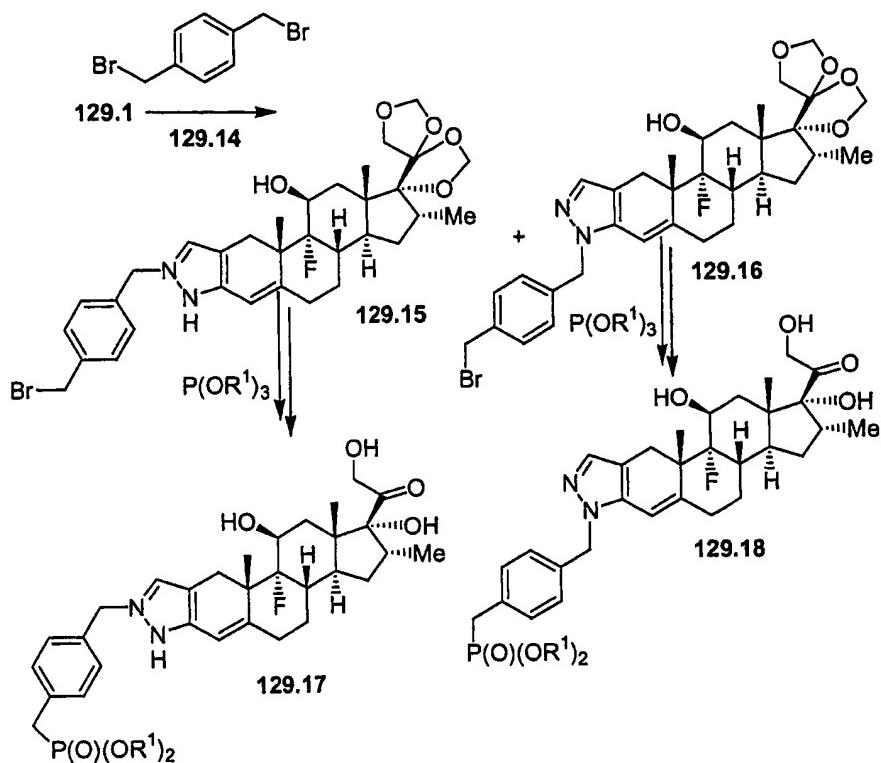
The preparation of dexamethasone phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is

- 5 illustrated above. In this procedure, the ketoaldehyde 128.2 is reacted with hydrazine, to afford the pyrazole derivative 129.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound 129.2, in which
 10 R^2 and X are as defined above, to yield the alkylation products 129.3 and 129.4. The alkylation of substituted pyrazoles is described, for example, in *Heterocyclic Chemistry*, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as
 15 dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products 129.3 and 129.4 are, except in cases where X is dialkylphosphono, converted

into the phosphonates **129.5** and **129.6**, using the procedures described herein, and deprotection then affords the triols **129.7** and **129.8**.



5 The preparation of representative compounds of the invention is illustrated above. The pyrazole **129.1** is reacted, as described above, with one molar equivalent of a dialkyl bromoacetyl phosphonate **129.9** (*Tet.*, 1978, 34, 649) to give the alkylated pyrazoles **129.10** and **129.11**. Deprotection then yields the triols **129.12** and **129.13**.



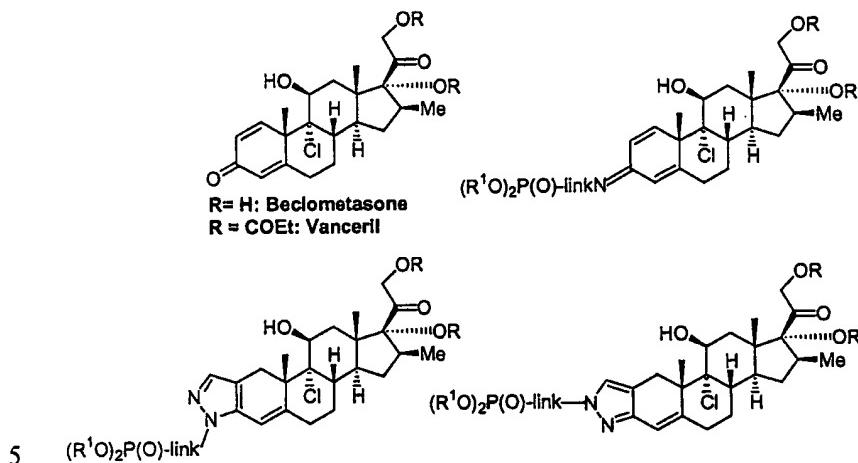
The preparation of representative compounds of the invention is illustrated above. The pyrazole 129.1 is reacted, as described above, with 1,4-bis(bromomethyl)benzene 129.14 to give the pyrazoles 129.15 and 129.16. The products are subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain, the phosphonates 129.17 and 129.18. The Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115-72. In the procedure, the substrate is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite. Using the above procedures, but employing, in place of the dibromide 129.14, different dibromides, the products analogous to 129.17 and 129.18 are obtained.

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Examples 130-133 – Beclomethasone Derivatives

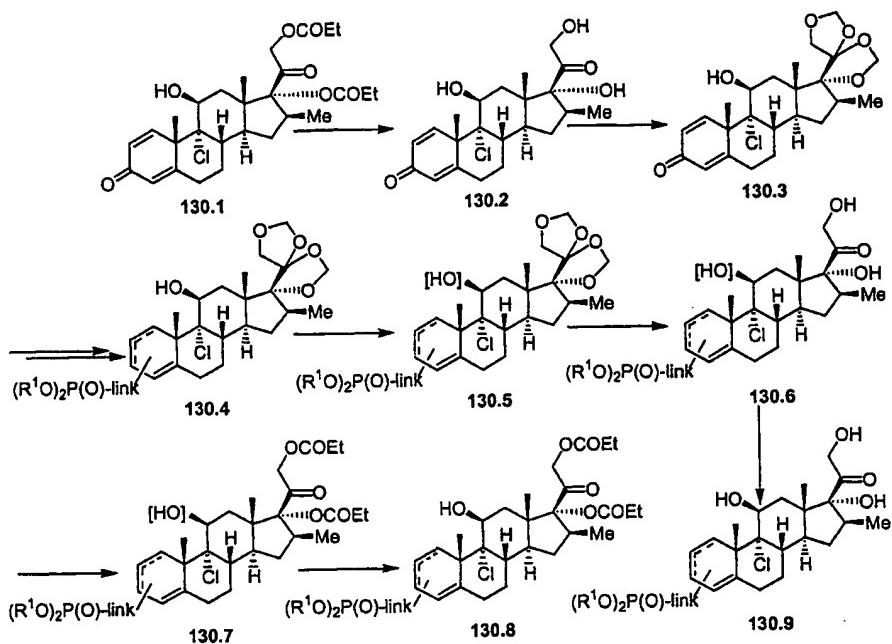
The structures of Beclomethasone (British Patent GB 912378) and Vanceril (US Patent 4024131) and representative phosphonate esters of the invention are shown below, in which the substituent R¹ is H, alkyl, alkenyl, aryl

or aralkyl. These compounds incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.



The synthesis of representative phosphonate derivatives of beclomethasone is outlined in Examples 130-133. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by 10 protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols 15 is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 130 Preparation of Representative Beclomethasone Derivatives



- 5 The preparation of representative beclomethasone derivatives of the invention is illustrated above. The propionate esters are hydrolyzed, for example by reaction with two molar equivalents of lithium hydroxide in aqueous dimethoxyethane solution at ambient temperature, to give the triol 130.2. The product is then reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative 130.3. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester 130.4. Prior to hydrolysis of the BMD protecting group, the 11-hydroxyl group is protected.
- 10 The protecting group is selected so that it is stable to the conditions required for removal of the BMD group, and so that it is removable without affecting the subsequently introduced 17, 21-diester moiety. For example, the 11-hydroxyl group is protected by conversion to the 4-azidobutyrate ester, by reaction with 4-azidobutyryl chloride in pyridine. The 11-azidobutyrate group is then removed
- 15 from the diester 130.7 by reaction with triphenylphosphine, as described in Bull. Soc. Chem. Jpn., 59, 1296, 1986. Alternatively, the 11-hydroxyl group is
- 20

protected by conversion to the 2-(trimethylsilyl)ethyl carbonate, by reaction with 2-(trimethylsilyl)ethyl carbonyl chloride and pyridine. The 2-(trimethylsilyl) carbonate is removed from the diester 130.7 by reaction with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in *Tet. Lett.*, 22, 969, 1981.

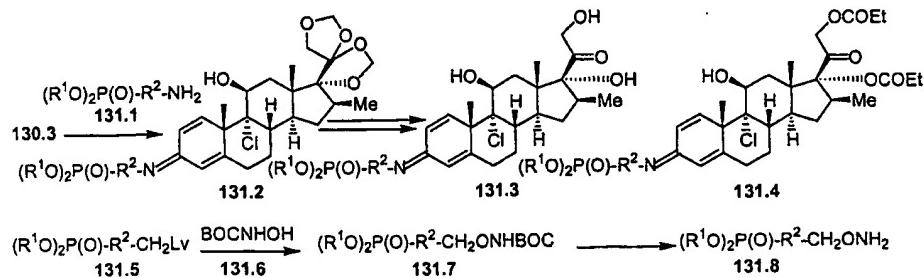
Alternatively, the 11-hydroxyl group is protected by conversion to the trichloroacetyl ester, by reaction with trichloroacetyl chloride in dimethylformamide-pyridine. The trichloroacetyl ester is removed by reaction with ethanolic ammonia at ambient temperature, as described in *Coll. Czech. Chem. Commun.*, 27, 2567, 1962.

The BMD moiety in the protected product 130.5 is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol 130.6. The latter compound is then acylated, for example by reaction with propionic acid and dicyclohexyl carbodiimide in dimethylformamide at ambient temperature, or by reaction with propionyl chloride and triethylamine in dichloromethane, to produce the dipropionate 130.7. Deprotection of the 11-hydroxyl group, as described above, then affords the diester 130.8. The protected 17,21-diol 130.8 is deprotected, as described above, to afford the 11,17,21 trihydroxy compound 130.9.

Alternatively, the 20-ketone group is protected as the diethylamine adduct by reaction with titanium tetrakis(diethylamide), as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 219.

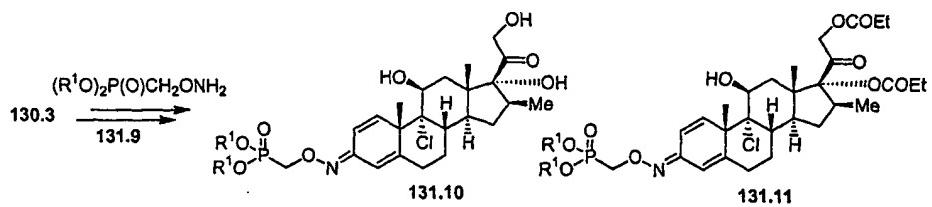
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Example 131 Preparation of Representative Beclomethasone Derivatives



The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative 130.3 is reacted with an amine or hydroxylamine 131.1, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, to afford the imine or iminoxy product 131.2. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, 1978, 86, 133. and in *J. Mass. Spectrom.*, 1995, 30, 497. The BMD-protected side-chain compound 131.2 is then converted into the diester 131.4 and the triol 131.3.

The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated above. In this procedure, a phosphonate 131.5, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 131.6 (Aldrich) to produce the ether 131.7. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine, to give the product 131.7. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 131.8.

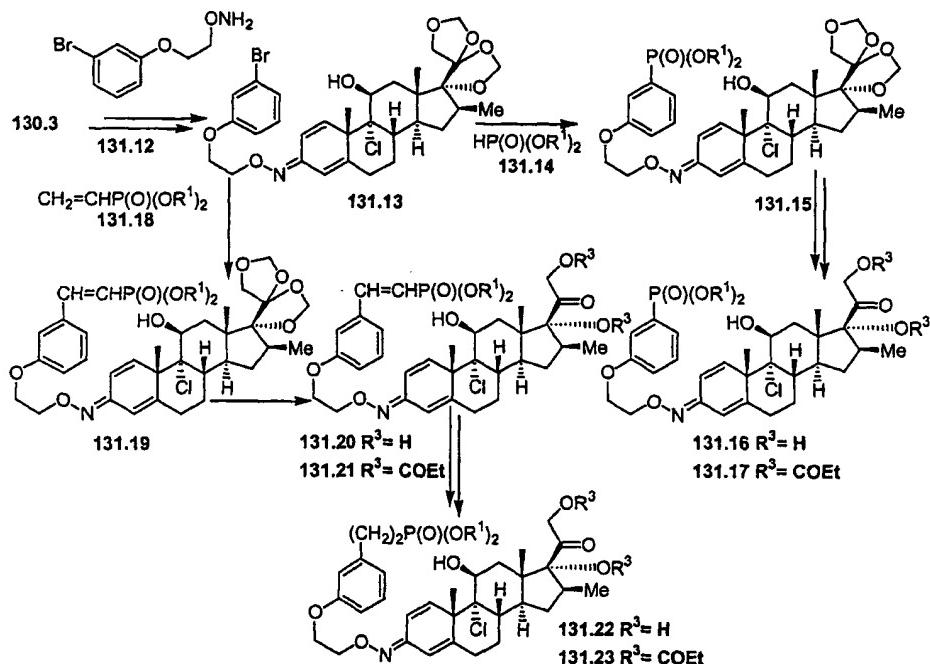


The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate

130.3 is reacted with a dialkyl phosphonomethyl hydroxylamine 131.9, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (Tet. Lett., 1986, 27, 1477) and BOC-hydroxylamine, to afford, after protection-deprotection and side chain acylation, the oxime ethers 131.10 and 131.11. The oxime forming reaction is performed at ambient temperature in pyridine solution between equimolar amounts of the reactants.

5 Using the above procedures, but employing, in place of the oxime ether 131.9, different oxime ethers 131.8, the corresponding products 131.3 and 131.4 are obtained.

10



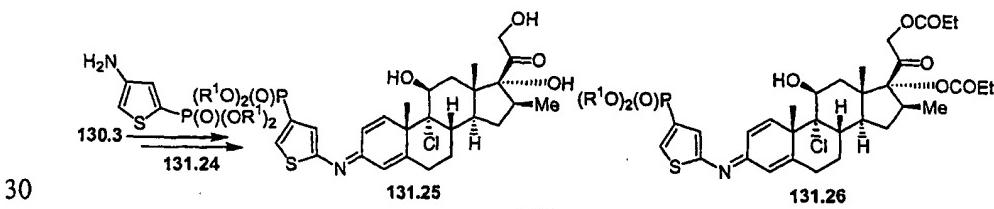
The preparation of phosphonates incorporating an iminoxy group, by means of the reaction between the substrate 130.3 and O-2-(3-bromophenoxy)ethoxyhydroxylamine 131.12, prepared as described above from 2-(3-bromophenoxy)ethyl bromide (French patent FR 1481052). The resultant oxime ether 131.13 is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite 131.14 to afford the phosphonate 131.15. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and 15 dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The reaction is 20

performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0). The BMD-protected product 131.15 is then converted into the triol 131.16 and the dipropionate 131.17.

- 5 Alternatively, the bromo-substituted product 131.13 is coupled, in a palladium-catalyzed Heck reaction, with a dialkyl vinyl phosphonate 131.18 (Aldrich) to give the unsaturated phosphonate 131.19. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, 10 p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)-palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium 15 carbonate. The product 131.19 is then converted into the triol 131.20 and the dipropionate 131.21.

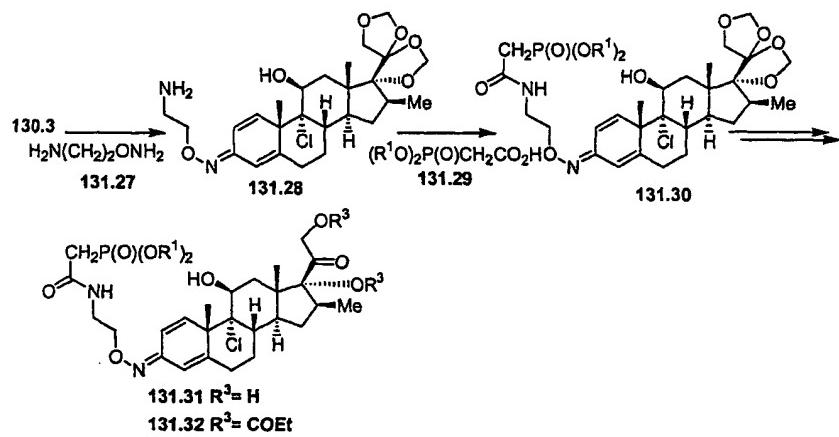
- Optional, the styrenoid double bond present in the products 131.20 and 131.21 is reduced, for example by reaction with diimide, to produce the saturated analogs 131.22 and 131.23.. The reduction of olefinic bonds is described in 20 Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

- Using the above procedures, but employing, in place of the 25 bromophenoxy reagent 131.12, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 131.16, 131.17, 131.20, 131.21, 131.22 and 131.23 are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate 130.3 is reacted with a dialkyl 4-amino-2-thienyl phosphonate 131.14, prepared by the palladium-catalyzed coupling reaction between a dialkyl phosphite and 2-bromo-4-aminothiophene (Tet., 1987, 43, 3295) to give, after deprotection and side chain acylation, the imine products 131.25 and 131.26. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions, to give the products 131.25 and 131.26.

Using the above procedures, but employing, in place of the 3-aminothienyl phosphonate 131.24 different amino-substituted aryl or heteroaryl phosphonates, products analogous to 131.25 and 131.26 are obtained.



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The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and an amide linkage is illustrated above. In this procedure, the dienone 130.3 is reacted with O-(2-aminoethyl)hydroxylamine 131.27 (Bioorganicheskaya Khim., 1986, 12, 1662) to yield the oxime 131.28. The reaction of steroidal 1,4-dien-3-ones with hydroxylamines is described in J. Steroid Bioch., 1976, 7, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then reacted with a dialkyl phosphonoacetic acid 131.29 (Aldrich), to yield the amide

oxime **131.30**. The preparation of amides from carboxylic acids and derivatives is described, for example, in *Organic Functional Group Preparations*, by

S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic

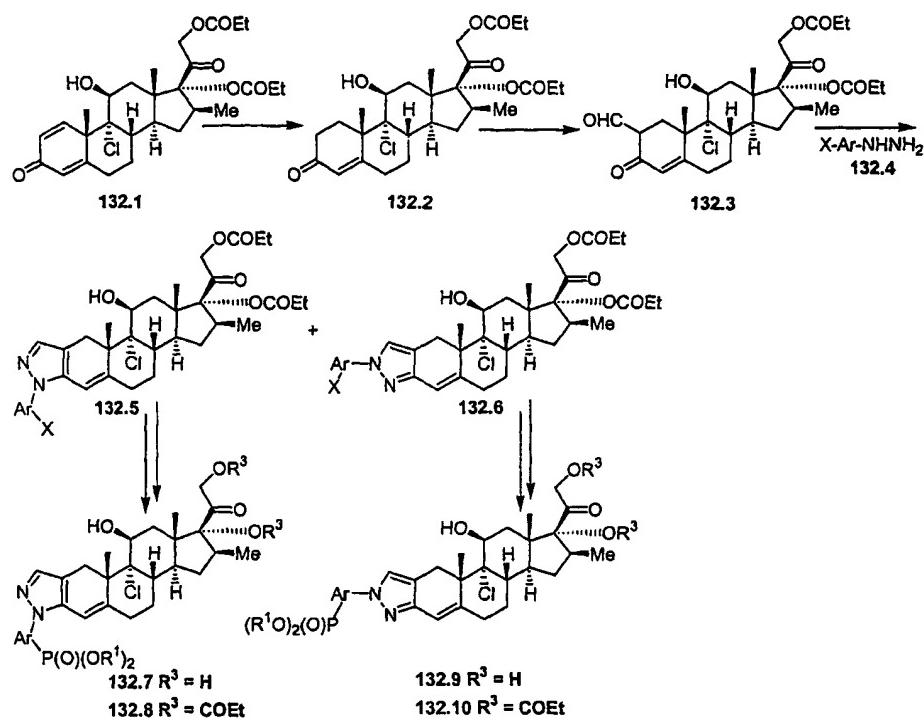
5 acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

10 Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolidine and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

15 The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

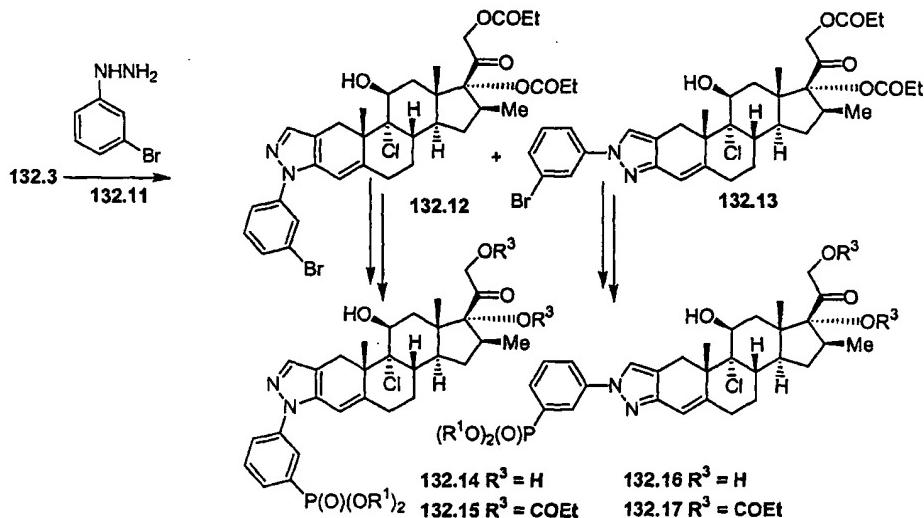
20 The amide product **131.30** is then converted into the triol **131.31** and the dipropionate **131.32**. Using the above procedures, but employing, in place of the hydroxylamine **131.27**, different amino-substituted hydroxylamines, and/or different carboxy-substituted phosphonates, the products analogous to **131.31** and **131.32** are obtained.

Example 132 Preparation of Representative Beclomethasone Derivatives



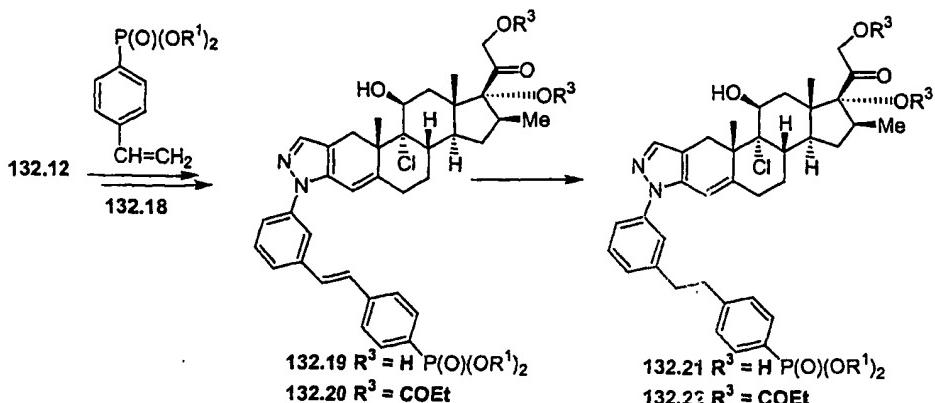
5 The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, Vanceril 132.1 is reduced to afford the 1,2-dihydro product, 132.2. The catalytic hydrogenation reaction is effected by the 10 use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in Australian Patent Application 275950409, to afford the 2-formyl product 132.3. Optionally, the substrate 132.1 is protected, 15 for example as described above, prior to the reduction and formylation reactions, as described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The 2-formyl product is then reacted with an aryl or heteroaryl hydrazine 132.4, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono,

bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles 132.5 and 132.6. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The pyrazoles 5 132.5 and 132.6 are then transformed, respectively, into the phosphonates 132.7, 132.8, 132.9 and 132.10.

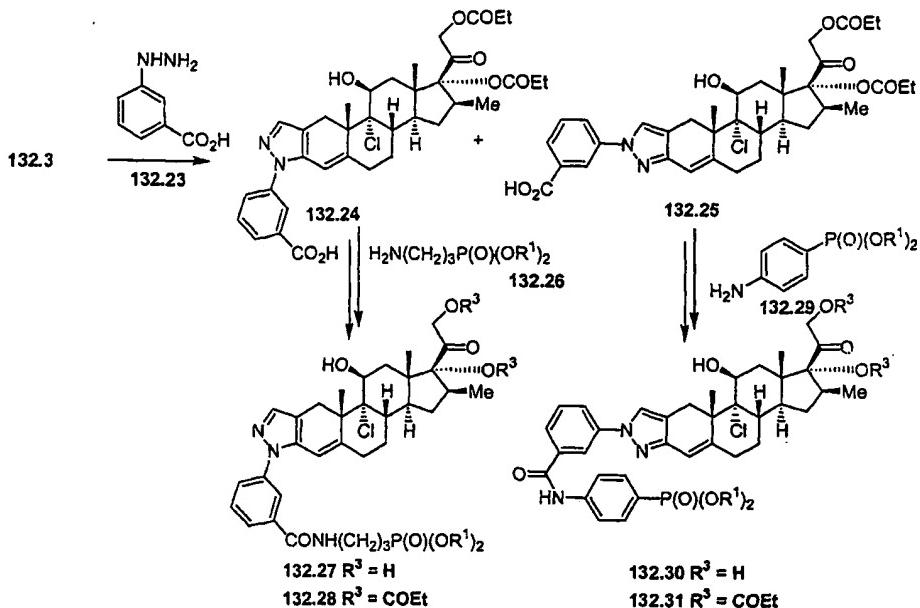


10 The preparation of phosphonates in which the phosphonate is attached by means of a phenyl group is illustrated above. In this sequence, the ketoaldehyde 132.3 is reacted, as described above, with 3-bromophenylhydrazine 132.11 (Fluka), to give the isomeric pyrazole products 132.12 and 132.13. The products are then reacted, as described above, with a dialkyl phosphite $\text{HP(O)(OR}^1\text{)}_2$ and 15 a palladium catalyst, to afford respectively the phosphonates 132.15 and 132.17. Basic hydrolysis, as described above, then yields the triols 132.14 and 132.16.

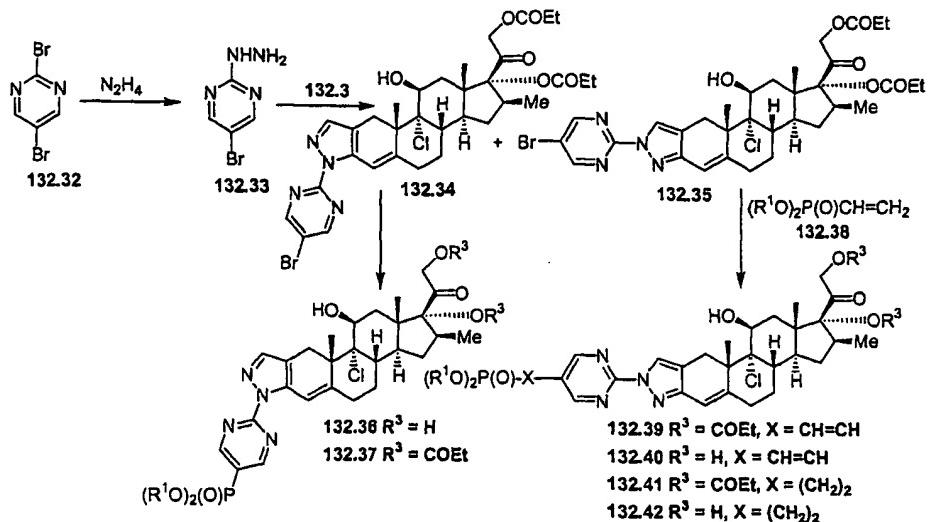
Using the above procedures, but employing, in place of 3-bromophenyl hydrazine, different bromoaryl or bromoheteroaryl hydrazines 132.4, the products analogous to 132.7, 132.8, 132.9 and 132.10 are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of an aromatic or heteroaromatic group and a saturated or unsaturated alkyl chain is illustrated above. In this procedure, the bromophenyl-substituted pyrazole 132.12 is coupled in a Heck reaction, as described above, with a dialkyl 4-vinylphenyl phosphonate 132.18 (*Macromolecules*, 1998, 31, 2918) to give the unsaturated phosphonate product 132.20. Basic hydrolysis then gives the triol 132.19. Optionally, the products are reduced, as described above, to give the saturated analogs 132.21 and 132.22. Application of the above procedures to the isomeric bromophenyl pyrazole 132.13 affords the products isomeric with 132.19, 132.20, 132.21 and 132.22. Using the above procedures, but employing, in place of the phosphonate 132.18, different dialkyl alkenyl phosphonates, and/or different bromoaryl or heteroaryl pyrazoles 132.5 or 132.6 (X = Br) the products analogous to 132.19, 132.20, 132.21 and 132.22 are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of an aryl or heteroaryl group and an amide linkage. In this procedure, 3-carboxyphenylhydrazine 132.23(Apin) is reacted in dimethylformamide solution at ambient temperature with the ketoaldehyde 132.3, to form the isomeric pyrazoles 132.24 and 132.25. The product 132.24 is then coupled, as described above, with a dialkyl 3-aminopropyl phosphonate 132.26 (Synthelec) to give the amide 132.27. Basic hydrolysis then produces the triol 132.27. Alternatively, the carboxylic acid 132.25 is reacted with a dialkyl 4-aminophenyl phosphonate 132.29 (Epsilon) to prepare the triol 132.30 and the diester 132.31. Using the above procedures, but employing, in place of the carboxy-substituted hydrazine 132.23, different carboxy-substituted aryl or heteroaryl hydrazines, the products analogous to 132.27, 132.28, 132.30 and 132.31 are obtained.

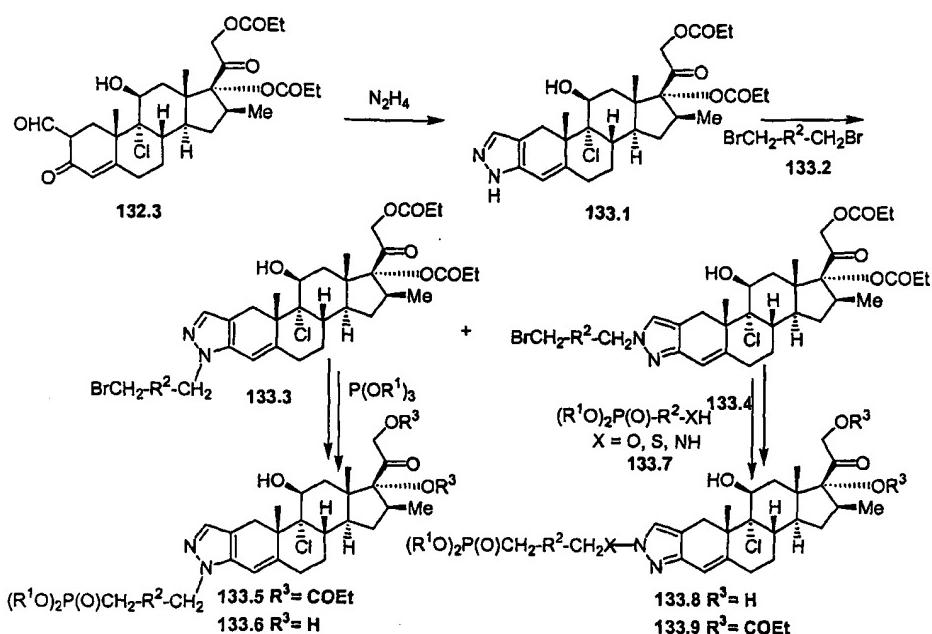


The preparation of phosphonates in which the phosphonate is attached by means of a pyrimidinyl group, either directly or with a saturated or unsaturated carbon chain is illustrated above. In this procedure, 2,5-dibromopyrimidine 132.32 (*Chem. Lett.*, 1992, 583) is reacted with hydrazine to afford 5-bromo-2-pyrimidinyl hydrazine 132.33. The preparation of pyrimidinyl hydrazines by the reaction of 2-halopyrimidines with hydrazine is described in *J. Med. Chem.*, 2002, 45, 5397. The product is then reacted with the ketoaldehyde 132.3 to yield the isomeric pyrazoles 132.34 and 132.35. The compound 132.34 is coupled, as described above, with a dialkyl phosphonate to afford the phosphonate 132.37; basic hydrolysis then gives the triol 132.36.

Alternatively, the isomeric pyrazole 132.35 is coupled, as described above, with a dialkyl vinyl phosphonate 132.38 to prepare the phosphonate 132.39. Basic hydrolysis then produces the triol 132.40, and reduction of the double bond, as described above, yields the diester 132.41 and the triol 132.42.

Using the above procedures, but employing, in place of the pyrimidinyl hydrazine 132.33, different bromo-substituted aryl or heteroaryl hydrazines, and/or different alkenyl phosphonates, the products analogous to 132.36, 132.37, 132.39, 132.40, 132.41 and 132.42 are obtained.

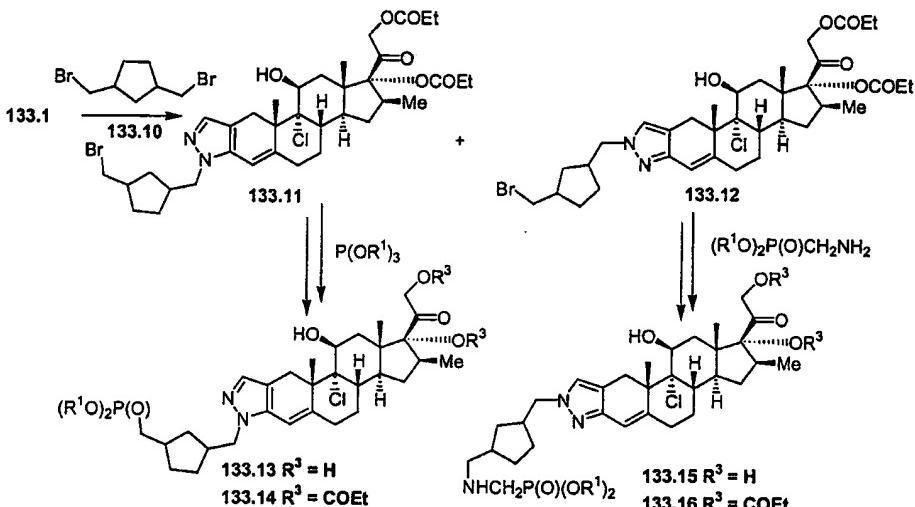
Example 133 Preparation of Representative Beclomethasone Derivatives



5 The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde 132.3 is reacted with hydrazine, to afford the pyrazole derivative 133.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in J. Am. Chem. Soc, 1964, 86, 1520. The reaction is 10 performed in acetic acid at ambient temperature. The resulting pyrazole is then reacted with a bis(bromomethyl) reagent 133.2, in which R² is as defined above, to produce the isomeric 2' and 1' alkylation products 133.3 and 133.4 respectively. The alkylation of substituted pyrazoles is described, for example, in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction 15 is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The isomer 133.3 is reacted, in an Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate 133.5: basic hydrolysis then gives the triol 133.6. The preparation 20 of phosphonates by means of the reaction between an alkyl halide and a trialkyl phosphite is described in Handb. Organophosphorus Chem., 1992, 115-72. The

substrate and an excess of the phosphite are heated at ca. 120° to effect the conversion. Application of the above procedure to the isomeric 1'-substituted pyrazole yields the corresponding isomeric products.

Alternatively, the bromomethyl-substituted pyrazole 133.4 is reacted
 5 with a dialkyl hydroxy, mercapto or amino-substituted phosphonate 133.7 to afford the ether, thioether or amine products 133.8 and 133.9. The displacement reaction is performed in a polar solvent such as dimethylformamide or acetonitrile, at from ambient temperature to about 70°, in the presence of an inorganic base such as potassium carbonate, or an organic base such as
 10 dimethylaminopyridine. Application of the above procedure to the isomeric 2'-substituted pyrazole yields the corresponding isomeric products.

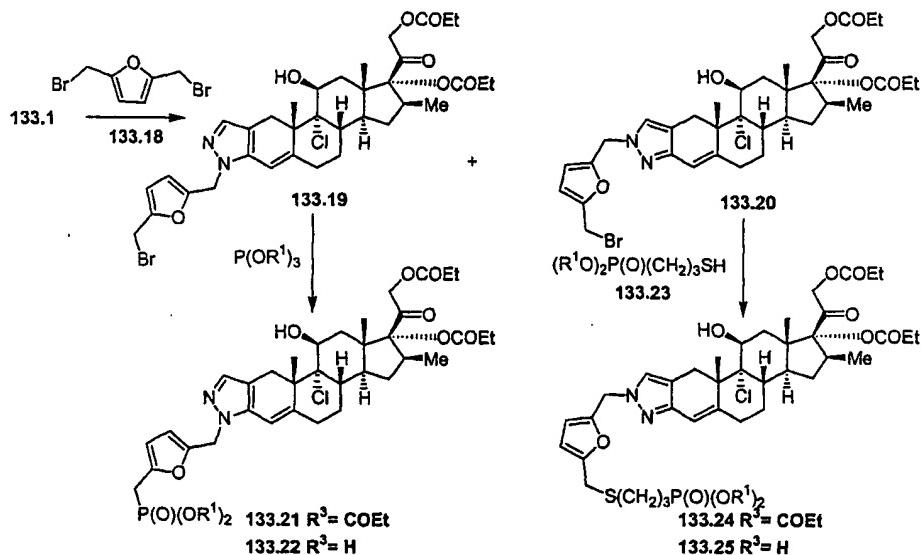


15 Representative compounds of the invention can be prepared as illustrated above. The pyrazole 133.1 is reacted, in dimethylformamide solution at ca. 90°, with a dialkyl 1,3-bis(bromomethyl)cyclopentane 133.10 (*Bull. Soc. Chim. Fr.*, 1975, 1295) and dimethylaminopyridine, to yield the isomeric alkylation products 133.11 and 133.12. The 2'-substituted compound 133.11 is then reacted
 20 with ten molar equivalents of a trialkyl phosphite at 100°, to yield the phosphonate 133.14. Basic hydrolysis produces the triol 133.13.

Alternatively, the 1'-substituted isomer 133.12 is reacted at 70° in dimethylformamide solution with one molar equivalent of a dialkyl aminomethyl

phosphonate 133.15 (Interchim) and potassium carbonate, to prepare the amine phosphonate 133.17; basic hydrolysis affords the triol 133.16. Application of the procedures to the isomeric bromomethyl compound 133.11 affords the corresponding isomeric products.

5

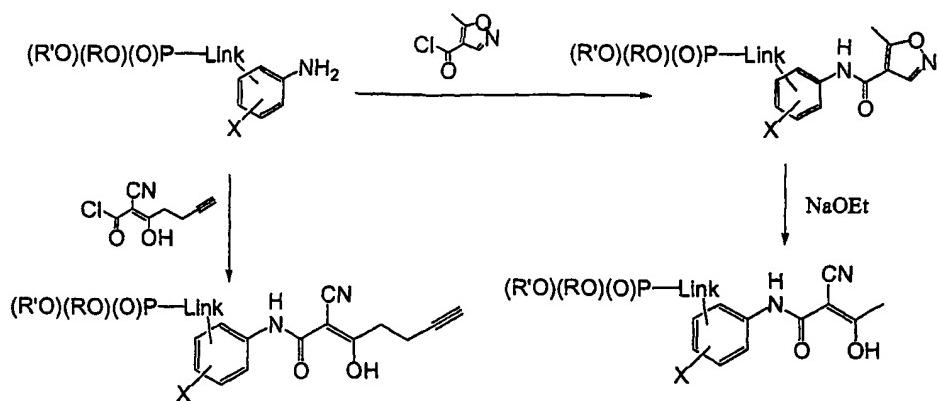


Representative compounds of the invention can be prepared as illustrated above. The pyrazole 133.1 is reacted, as described above, with 2,5-bis(bromomethyl)furan 133.18 (Tet., 1999, 55, 4709) to give the substituted pyrazoles 133.19 and 133.20. The 2'-substituted compound 133.19 is then reacted, as described above, with a trialkyl phosphite to produce the diester phosphonate 133.21 and the triol 133.22.

Alternatively, the 1' isomer 133.20 is reacted, as described above, with a dialkyl 3-mercaptopropyl phosphonate 133.23 (WO 2000077101) to give the diester 133.24 and the triol 133.25.

Using the above procedure, but employing, in place of the mercaptoethyl phosphonate 133.23, different hydroxy, mercapto or amino-substituted phosphonates, the corresponding ether, thioether or amino products are obtained.

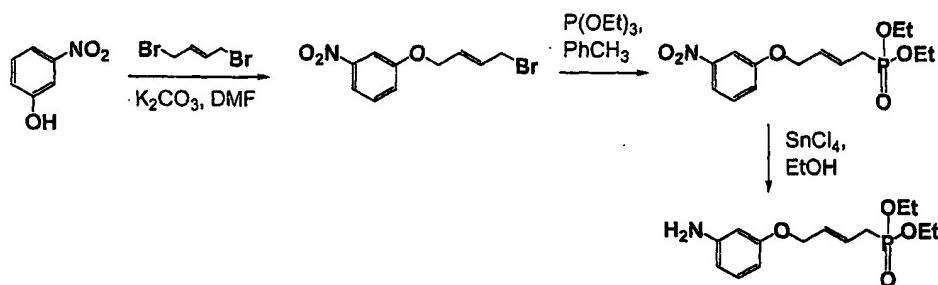
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Example 134 Preparation of Representative Compounds of the Invention

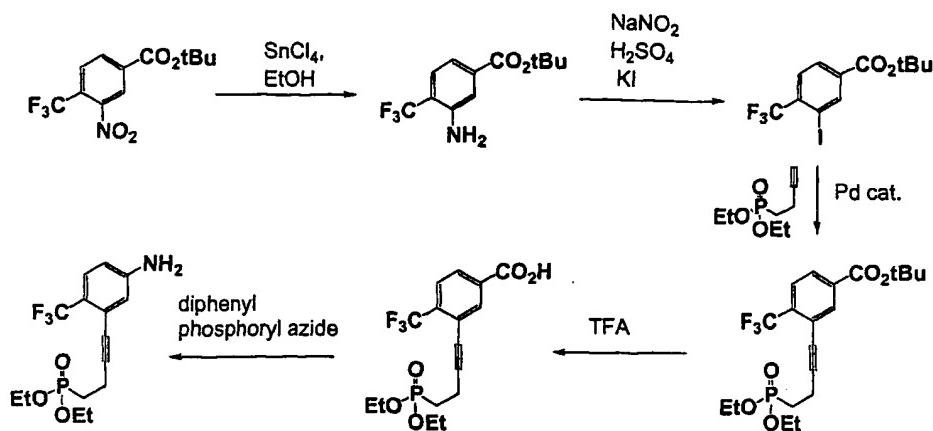
5 Representative compounds of the invention can be prepared as illustrated above. Synthetic methodology towards compounds such as these is described by Westwood et al, *J. Med. Chem.*, 1996, 39, 4608-4621.

The preparation of an intermediate aniline useful in the above general procedures is illustrated below.

10



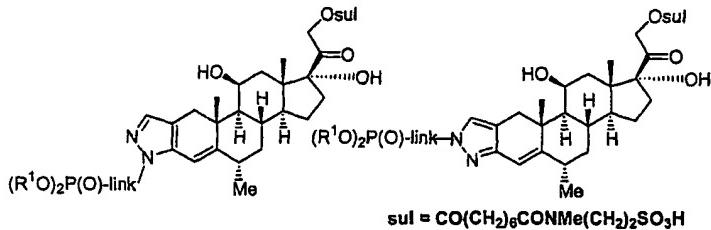
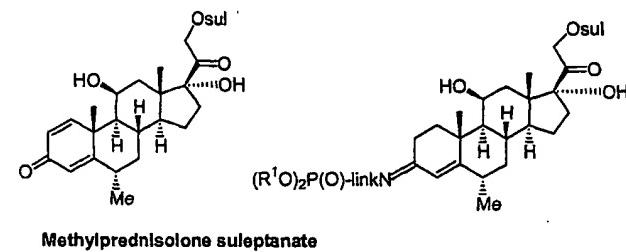
The preparation of an intermediate alkyne that can also be used in the above general procedures is illustrated below.



Examples 135-138 – Methylprednisolone Suleptanate Derivatives

The structures of Methylprednisolone suleptanate (WO 8900558) and

- 5 representative phosphonate esters of the invention are shown below, in which the substituent R¹ is H, alkyl, alkenyl, aryl or aralkyl. These compounds incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.

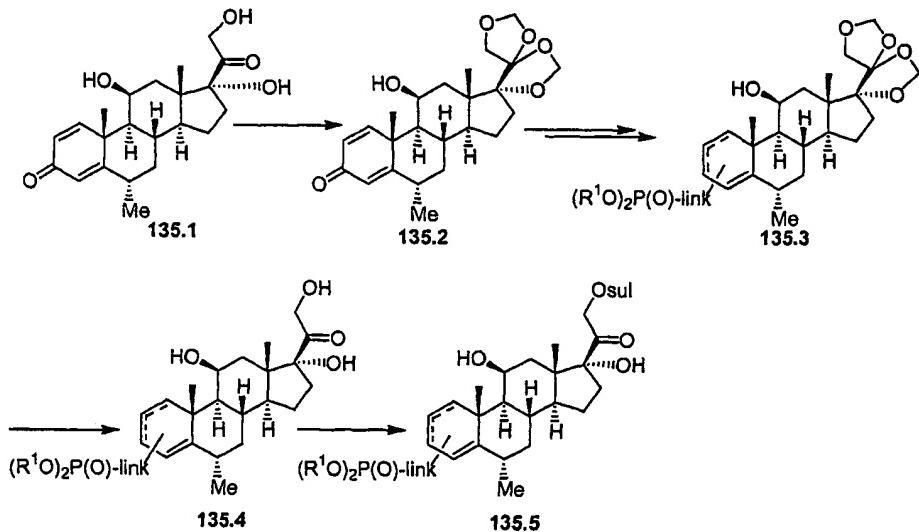


10

- The synthesis of representative phosphonate derivatives of methylprednisolone suleptanate is outlined in Examples 135-138. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect

the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal 5 ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

10 **Example 135 Preparation of Representative Methylprednisolone Suleptanate Derivatives**

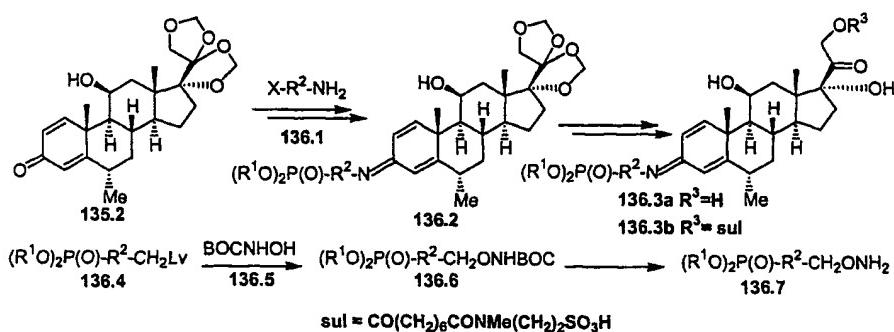


15 Representative compounds of the invention can be prepared as illustrated above. The steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, methylprednisolone **135.1** is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative **135.2**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester **135.3**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in Protective 20

Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol 135.4. The triol is then converted into the 21-suleptanate ester as described in WO 8900558. In this procedure, a mixed anhydride prepared by reacting suleptanic acid with pivaloyl chloride, in the presence of a base such as triethylamine, is reacted with the 21-hydroxy steroid 135.4 to prepare the 21-suleptanate ester 135.5.

Example 136 Preparation of Representative Methylprednisolone Suleptanate Derivatives

10

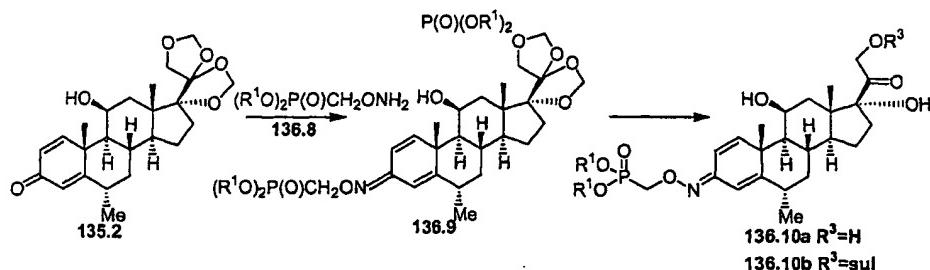


The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative 135.2 is reacted with an amine or hydroxylamine 136.1, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, 1978, 86, 133. and in *J. Mass. Spectrom.*, 1995, 30, 497. The BMD-protected side-

chain compound 136.2 is then converted into the triol 136.3a, and then to the suleptanate 136.3b.

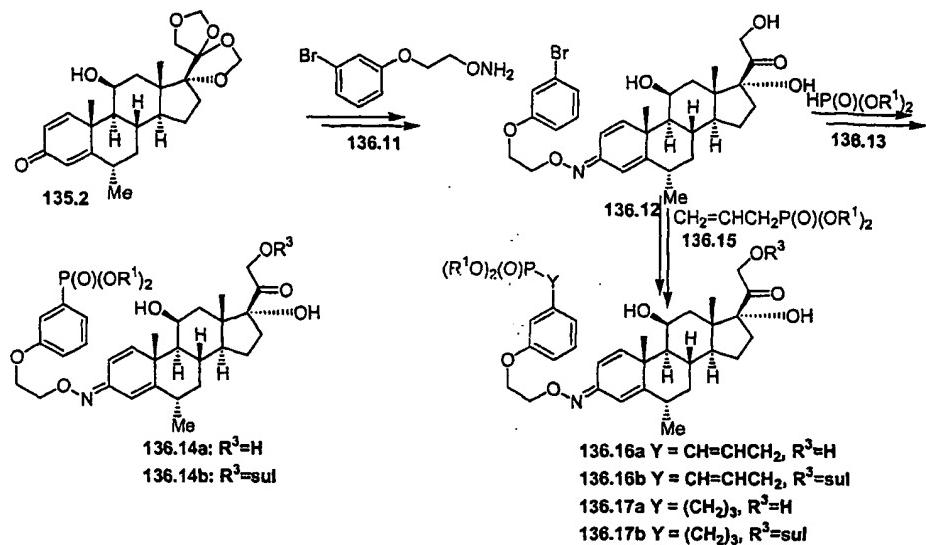
The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate 136.4, in which

- 5 Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 136.5 (Aldrich) to produce the ether 136.6. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for
 10 example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 136.7.



- 15 The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate 135.2 is reacted with a dialkyl phosphonomethyl hydroxylamine 136.8, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tet. Lett.*, 1986, 27, 1477) and BOC-hydroxylamine, to afford the
 20 oxime 136.9 which is deprotected to afford the triol 136.10a from which the suleptanate ester 136.10b is prepared. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

- Using the above procedures, but employing, in place of the
 25 hydroxylamine ether 136.8, different oxime ethers 136.1, the corresponding products 136.3b are obtained.



The preparation of compounds in which the phosphonate group is attached by means of a phenoxyethoxy oxime group is illustrated above. In this procedure, the dienone 135.2 is reacted, as described above, with O-(3-

- 5 bromophenoxyethyl)hydroxylamine **136.11**, prepared as described above from 3-bromophenoxyethyl bromide (FR 1481052) and BOC-protected hydroxylamine, to give, after deprotection of the side-chain, the oxime **136.12**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **136.13** to afford the phosphonate **136.14a**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0). The 21-hydroxy group is then converted into the 21-suleptanate product **136.14b**.

10

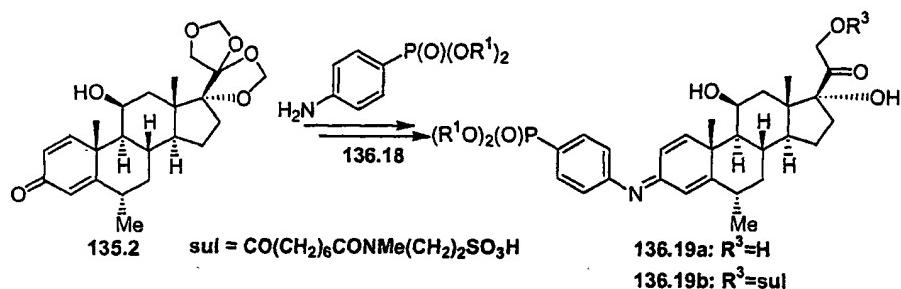
15 Alternatively, the bromo compound **136.12** is coupled with a dialkyl propenylphosphonate **136.15** (Aldrich) to afford the phosphonate **136.16a**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The 20 aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as

palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 136.16a is reduced, for example by reaction with diimide, to produce the saturated analog 136.17a. The reduction of olefinic bonds is

5 described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane. The products 136.16a and 136.17a are then converted into the suleptanate esters 136.16b and 136.17b.

10 Using the above procedures, but employing, in place of the bromophenoxyethoxy reagent 136.11, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 136.14b, 136.16b and 136.17b are obtained.

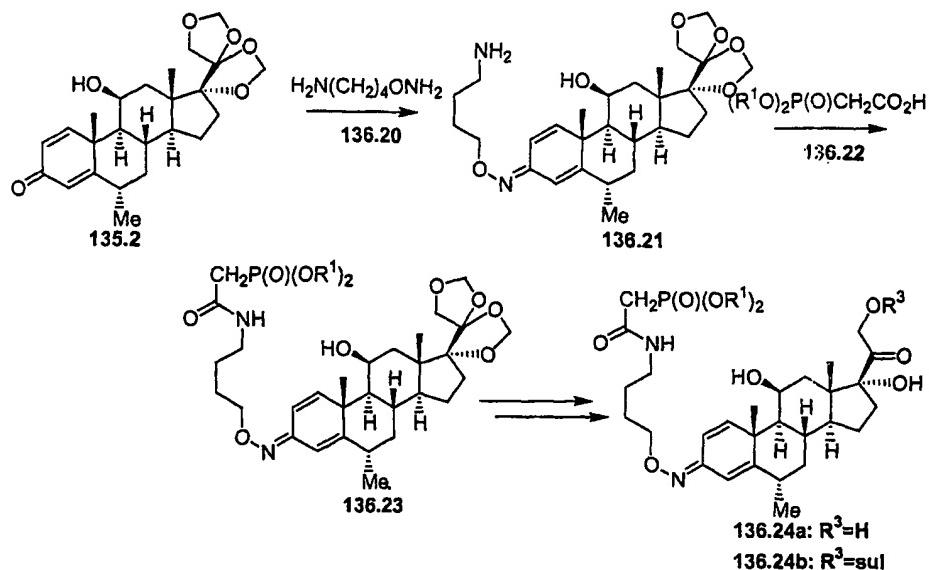
15



The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate

20 135.2 is reacted with a dialkyl 4-aminophenyl phosphonate 136.18, (Epsilon) to give, after deprotection, the imine product 136.19a. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. The product is then 25 converted into the suleptanate ester 136.19b.

Using the above procedures, but employing, in place of the 4-aminophenyl phosphonate 136.18 different amino-substituted aryl or heteroaryl phosphonates, products analogous to 136.19b are obtained.



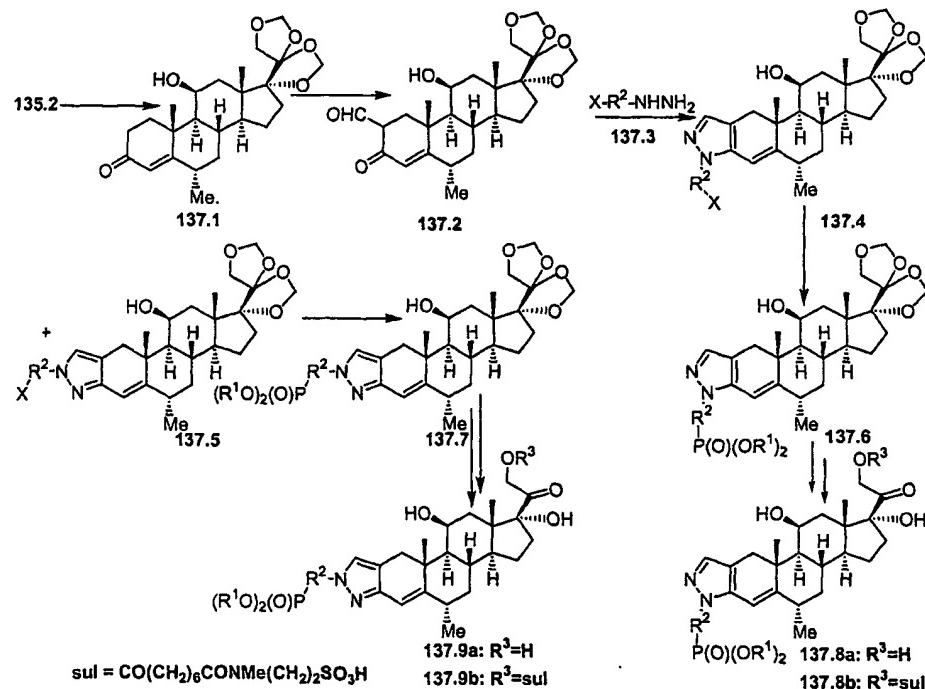
The preparation of phosphonates in which the phosphonate is attached by

- 5 means of an oximino group and an amide linkage is illustrated above. In this procedure, the dienone 135.2 is reacted with O-(4-aminobutyl)hydroxylamine 136.20 (Pol. J. Chem., 1981, 55, 1163) to yield the oxime 136.21. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in J. Steroid Bioch., 1976, 7, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then coupled with a dialkyl phosphonoacetic acid 136.22 (Aldrich), to yield the amide oxime 136.23. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by
- 10 S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-
- 15 hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.
- 20

Alternatively, the carboxylic acid is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. The amide product 136.23 is then converted into the suleptanate 136.24b.

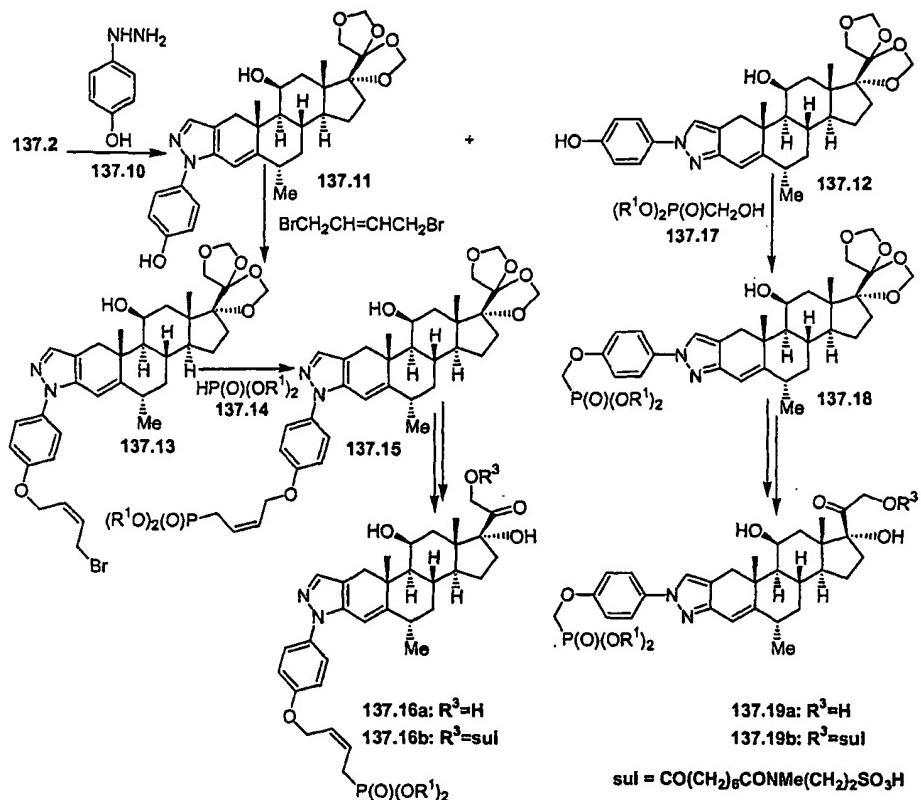
10 Using the above procedures, but employing, in place of the hydroxylamine 136.22, different amino-substituted hydroxylamines, and/or different carboxy-substituted phosphonates, the products analogous to 136.24b are obtained.

15 Example 137 Preparation of Representative Methylprednisolone Suleptanate Derivatives



The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, the BMD-protected dienone **135.2** is reduced 5 to afford the 1,2-dihydro product **137.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in J. Med. Chem., 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in J. Am. Chem. Soc., 1964, 86, 10 1520, to afford the 2-formyl product **137.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine **137.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 15 2'- and 1'-aryl pyrazoles **137.4** and **137.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in J. Am. Chem. Soc., 1964, 86, 1520. The pyrazoles **137.4** and **137.5** are then transformed via the BMD-protected intermediates **137.6** and **137.7**, into the phosphonate suleptanates **137.8b** and **137.9b**.

20



The preparation of phosphonates in which the phosphonate is attached by means of a phenyl ring and an alkoxy or an alkenyl linkage is illustrated above.

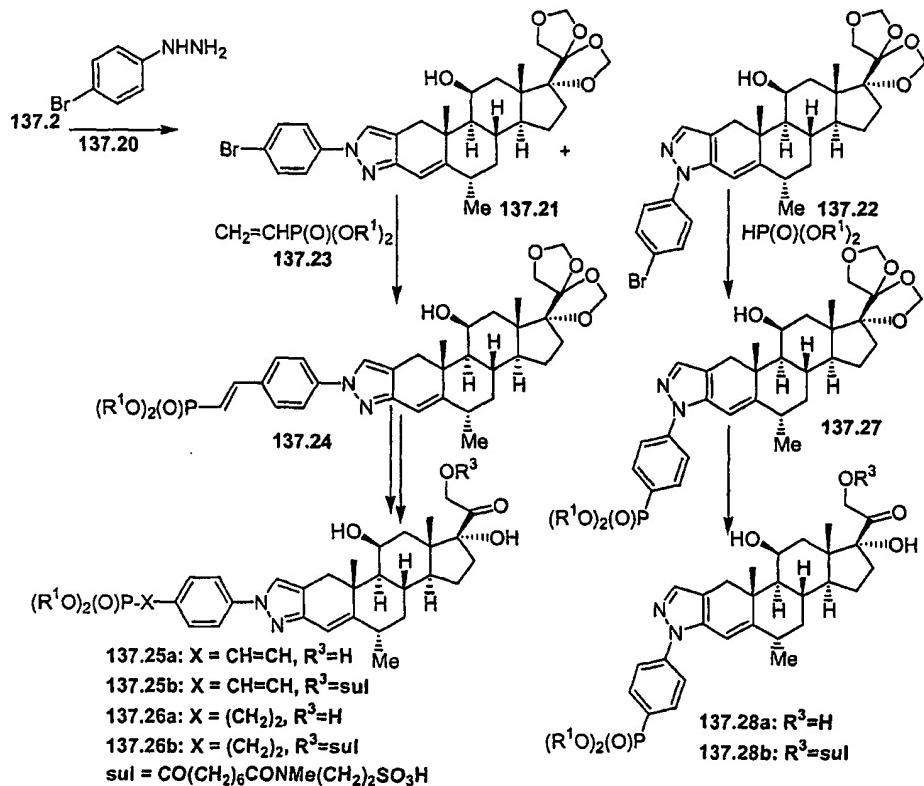
- 5 In this procedure, the ketoaldehyde 137.2 is reacted, as described above, with 4-hydroxyphenylhydrazine 137.10 (Epsilon) to give the pyrazoles 137.11 and 137.12. The 2'-substituted isomer 137.11 is then reacted in dimethylformamide solution at ambient temperature with one molar equivalent of 1,4-dibromobut-2-ene and dimethylaminopyridine, to yield the bromoether 137.13. The product is
10 then reacted at 120° in an Arbuzov reaction with a trialkyl phosphite 137.14 to give the phosphonate product 137.15. The Arbuzov reaction, in which an alkyl bromide is transformed into the corresponding phosphonate, by heating at from 60° to about 150° with a trialkyl phosphite, is described in Handb.
Organophosphorus Chem., 1992, 115-72. The BMD protecting group is then
15 removed and the product is acylated to yield the suleptanate ester 137.16b.

Alternatively, the 1'-substituted pyrazole 137.12 is reacted, in a Mitsonobu reaction, with a dialkyl 2-hydroxymethyl phosphonate 137.17

(Aldrich) to afford the ether **137.18**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p.

- 5 153-4 and in Org. React., 1992, 42, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The product **137.18** is then
10 deprotected to give the triol **137.19a**, and the latter compound is acylated to afford the suleptanate **137.19b**.

Using the above procedures, but employing different dibromides or hydroxyl-substituted phosphonates, the products analogous to **137.16b** and **137.19b** are obtained. The functionalization procedures are interchangeable
15 between the pyrazole substrates **137.11** and **137.12**.



The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl ring or a phenyl ring and a saturated or unsaturated carbon chain is illustrated above. In this procedure, the ketoaldehyde 137.2 is reacted, as described above, with 4-bromophenyl hydrazine 137.20 (*J.*

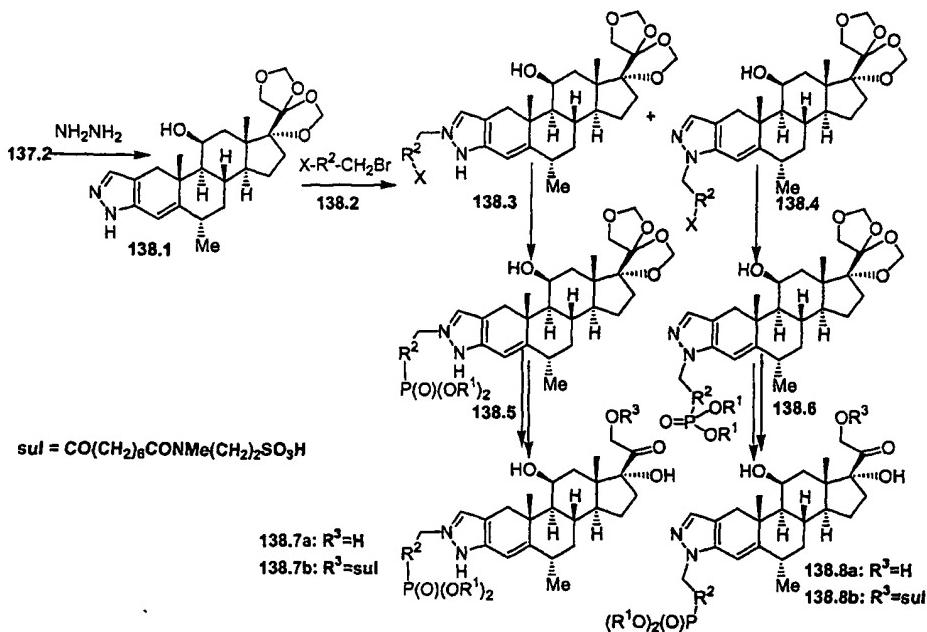
- 5 *Organomet. Chem.*, 1999, 62, 581) to produce the pyrazoles 137.21 and 137.22. The 1'-substituted isomer 137.21 is coupled, in the presence of a palladium catalyst, with a dialkyl vinylphosphonate 137.23(Aldrich) to give the phosphonate 137.24. The product is then deprotected to afford the triol 137.25a which is converted into the suleptanate 137.25b. Optionally, the styrenoid
- 10 double bond present in the product 137.25b is reduced, as described above, to produce the saturated analog 137.26b.

Alternatively, the 2'-substituted pyrazole 137.22 is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite to prepare the phosphonate 137.27 which is deprotected, and the product is acylated to give the

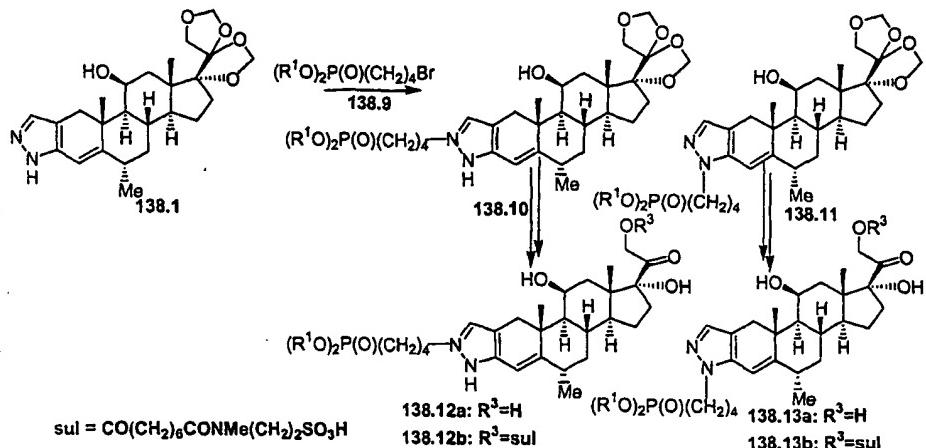
15 suleptanate ester 137.28b. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and tetrakis(triphenylphosphine)palladium(0).

- 20 Using the above procedures, but employing, in place of the bromophenyl hydrazine 137.20, different bromo-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 137.25b, 137.26b and 137.28b are obtained.

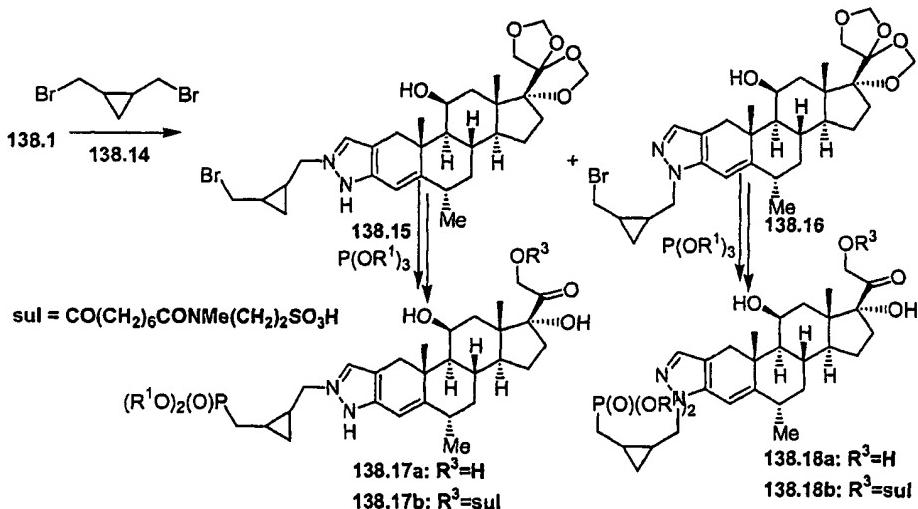
- 25 **Example 138 Preparation of Representative Methylprednisolone Suleptanate Derivatives**



The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In 5 this procedure, the ketoaldehyde 137.2 is reacted with hydrazine, to afford the pyrazole derivative 138.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound 138.2, in which R^2 and X are as defined above, to yield the alkylation products 138.3 and 138.4. The alkylation of substituted pyrazoles is described, for example, in *Heterocyclic Chemistry*, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as 10 dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products 138.3 and 138.4 are, except in cases where X is dialkylphosphono, converted into the phosphonates 138.5 and 138.6, using the procedures described herein, and deprotection/acylation then affords the suleptanate esters 138.7b and 138.8b. 15



Representative compounds of the invention can be prepared as illustrated above. The pyrazole 138.1 is reacted in tetrahydrofuran solution, as described above, with one molar equivalent of a dialkyl bromobutyl phosphonate 138.9 (*Synthesis*, 1994, 9, 909) and lithium hexamethyldisilazide to give the alkylated pyrazoles 138.10 and 138.11. Deprotection/acylation then yields the suleptanates 138.12b and 138.13b.



10

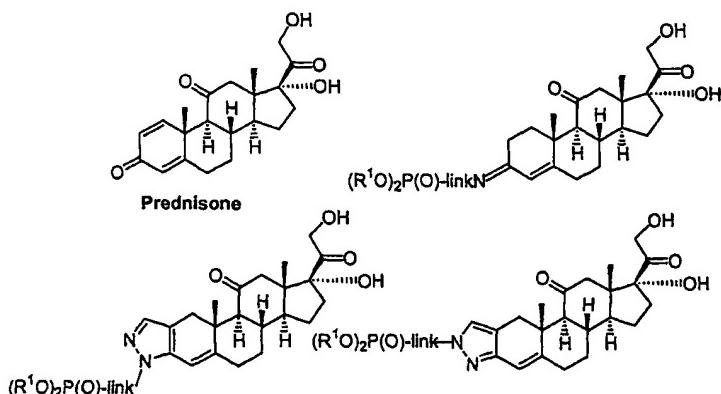
Representative compounds of the invention can be prepared as illustrated above. The pyrazole 138.1 is reacted in tetrahydrofuran solution, as described above, with 1,2-bis(bromomethyl)cyclopropane 138.14 (*Tet.*, 1997, 53, 10459) to give the pyrazoles 138.15 and 138.16. The products are subjected to an

Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain and acylation, the suleptanate phosphonates 138.17b and 138.18b. The Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115-72. In the procedure, the substrate is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite.

Using the above procedures, but employing, in place of the dibromide 138.14, different dibromides, the products analogous to 138.17b and 138.18b are obtained.

Examples 139-142 – Prednisone Derivatives

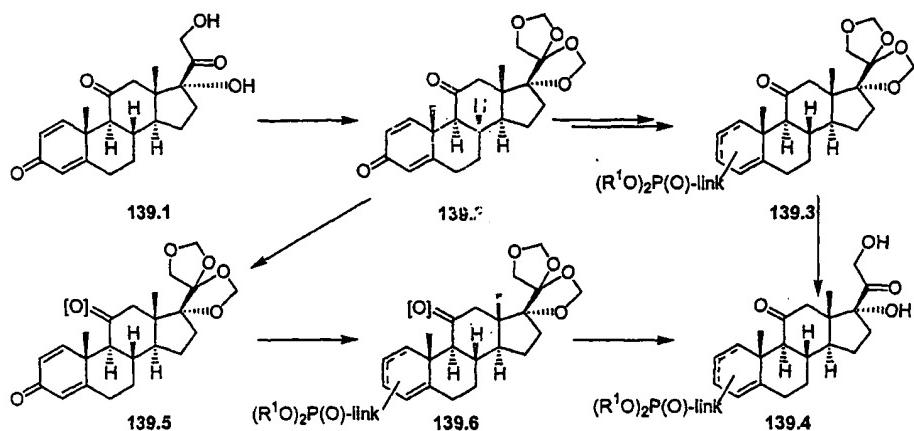
The structures of prednisone (US Patent 2897464) and representative phosphonate esters of the invention are shown below, in which the substituent R¹ is H, alkyl, alkenyl, aryl or aralkyl. These compounds incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.



20

The synthesis of representative phosphonate derivatives of prednisone is outlined in Examples 139-142. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection

of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van 5 Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 139 Preparation of Representative Prednisone Derivatives

5 Representative compounds of the invention can be prepared as illustrated above. The steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, prednisone is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative 139.2. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester 139.3. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol 139.4. Optionally, depending on the nature of the reactions to be employed, the 11-ketone group in the BMD compound 139.2 is protected before introduction of the phosphonate group. The ketone is protected, for example, as the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in J. Am. Chem. Soc., 77, 1904, 1955. Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in J. Chem. Soc., Chem. Comm., 1351, 1987.

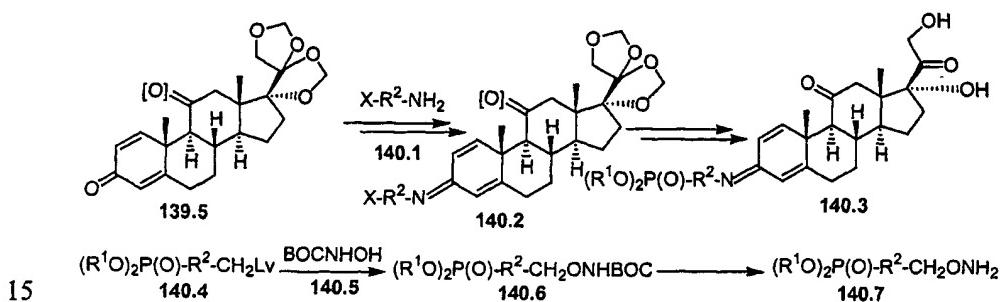
20 Alternatively, the 11-ketone is protected by conversion to the N,N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone 139.2 with N,N-dimethylhydrazine in ethanol-acetic acid, as described in

Org. Syn., 50, 102, 1970. The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, 101, 5841, 1979.

Alternatively, the 11-ketone is protected as the diethylamine adduct. In
 5 this procedure, the substrate 139.2 is reacted with titanium
 tetrakis(diethylamide), as described in *J. Chem. Soc., Chem. Comm.*, 406, 1983,
 to afford the adduct. The ketone is deprotected by reaction with water in an
 aqueous organic solvent.

The 11-protected BMD compound 139.5 is then converted, using the procedures described below, into the phosphonate 139.6. Deprotection then yields the 11-keto diol 139.4.

Example 140 Preparation of Representative Prednisone Derivatives

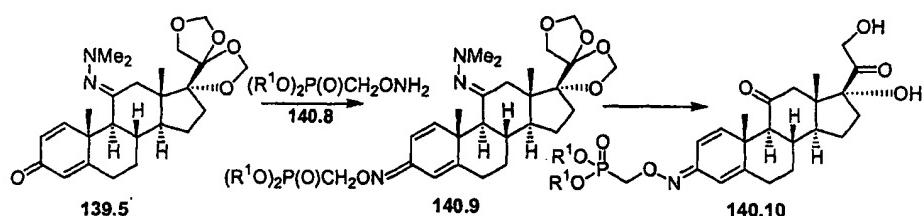


The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the doubly-protected derivative 139.5 is reacted with an amine or hydroxylamine 140.1, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic

solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, 1978, 86, 133. and in *J. Mass. Spectrom.*, 1995, 30, 497. The protecting groups are 5 then removed to afford the ketodiol 140.3.

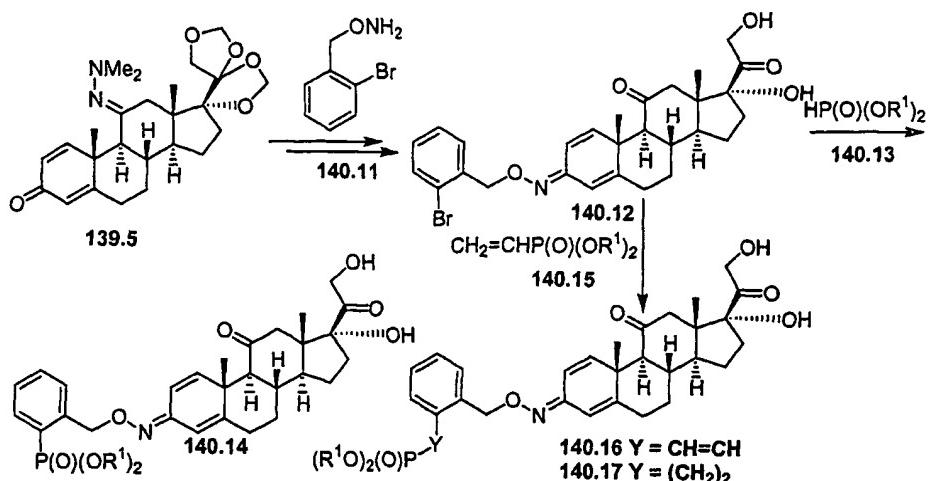
The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate 140.4, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 140.5 (Aldrich) to produce the ether 140.6. The 10 reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 140.7.

15



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate 20 139.5, in which the 11-ketone is protected as the dimethyl hydrazone, is reacted with a dialkyl phosphonomethyl hydroxylamine 140.8, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tet. Lett.*, 1986, 27, 1477) and BOC-hydroxylamine, to afford the oxime 140.9 which is deprotected by reaction with 50% aqueous acetic acid, to afford the diol 140.10. 25 The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether 140.8, different oxime ethers 140.1, the corresponding products 140.3 are obtained.



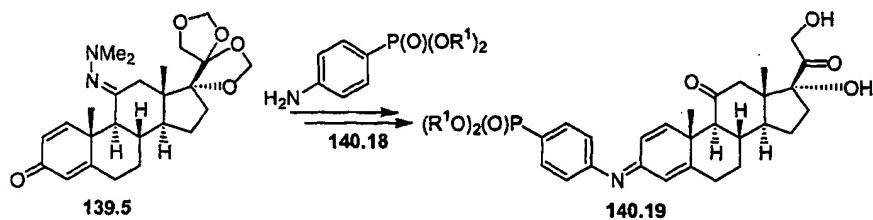
The preparation of compounds in which the phosphonate group is

- 5 attached by means of a benzyloxime group is illustrated above. In this procedure, the dienone **139.5** is reacted, as described above, with O-(2-bromobenzyl)hydroxylamine **140.11**, prepared as described above from 2-bromobenzyl bromide, to give, after deprotection, the oxime **140.12**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **140.13** to afford the phosphonate **140.14**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

- 10 **140.12** Alternatively, the bromo compound **140.12** is coupled with a dialkyl vinylphosphonate **140.15** (Aldrich) to afford the phosphonate **140.16**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The **140.12** aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond

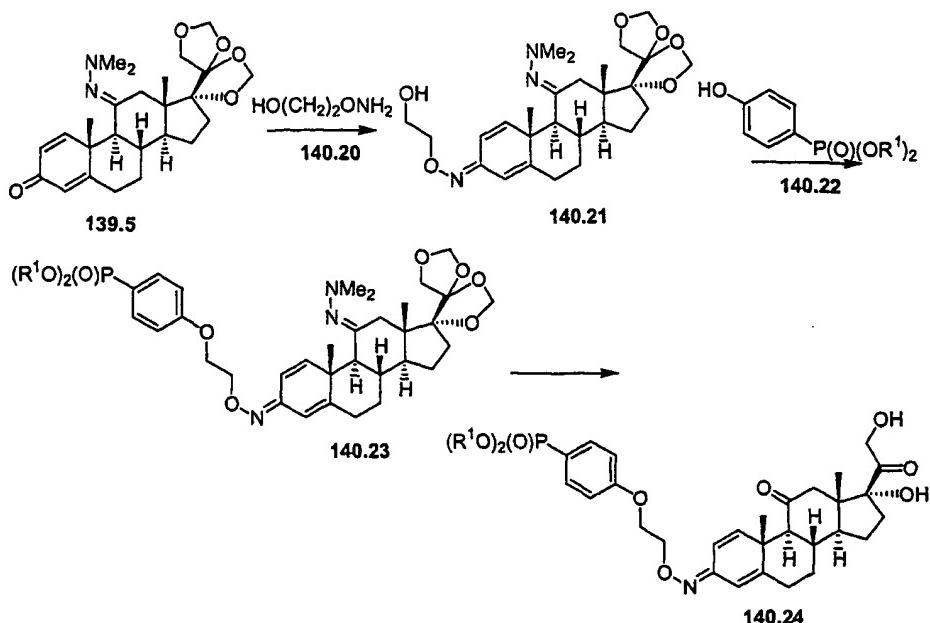
present in the product **140.16** is reduced, for example by reaction with diimide, to produce the saturated analog **140.17**. The reduction of olefinic bonds is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, 5 for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the benzyloxy reagent **140.11**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products 10 analogous to the compounds **140.14**, **140.16** and **140.17** are obtained.



The preparation of phosphonates in which the phosphonate is attached by 15 means of an imino group is illustrated above.. In this procedure, the substrate **139.5** is reacted with a dialkyl 4-aminophenyl phosphonate **140.18**, (Epsilon) to give, after deprotection, the imine product **140.19**. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such 20 as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-aminophenyl phosphonate **140.18** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **140.19** are obtained.



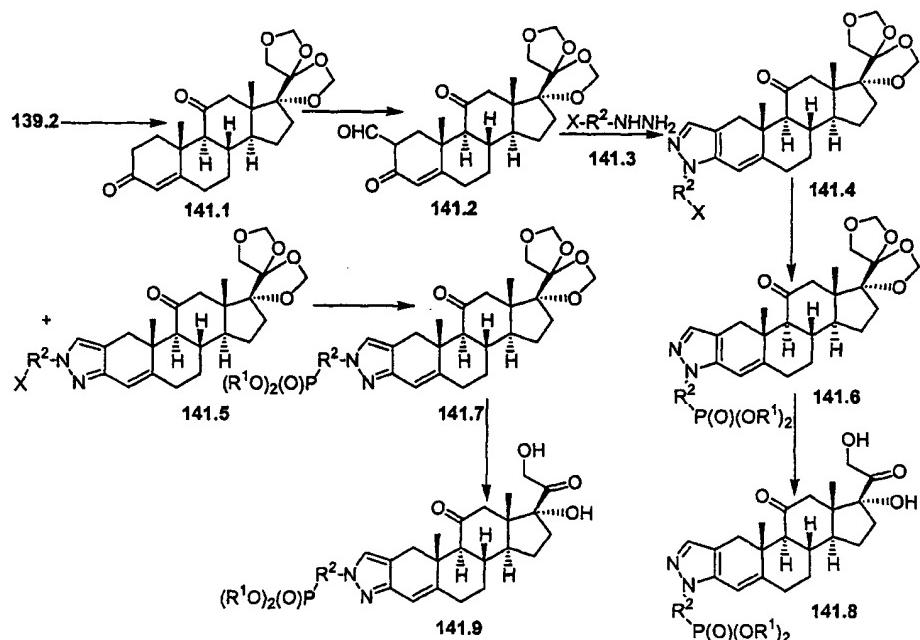
The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and an ether linkage is illustrated above. In this

- 5 procedure, the dienone 139.5 is reacted with O-(2-hydroxyethyl)hydroxylamine 140.20 (*J. Chem. Soc., Chem. Comm.*, 1986, 903) to yield the oxime 140.21. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, 1976, 7, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or
- 10 methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then reacted in a Mitsonobu reaction with a dialkyl 4-hydroxyphenyl phosphonate 140.22 (Epsilon), to yield the ether oxime 140.23. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p.
- 15 448, and in *Advanced Organic Chemistry*, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in *Org. React.*, 1992, 42, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether
- 20 products. The procedure is also described in *Org. React.*, 1992, 42, 335-656. The ether product 140.23 is then converted into the ketodiol 140.24.

Using the above procedures, but employing, in place of the hydroxylamine 140.20, different hydroxy-substituted hydroxylamines, and/or different hydroxy-substituted aryl phosphonates, the products analogous to 140.24 are obtained.

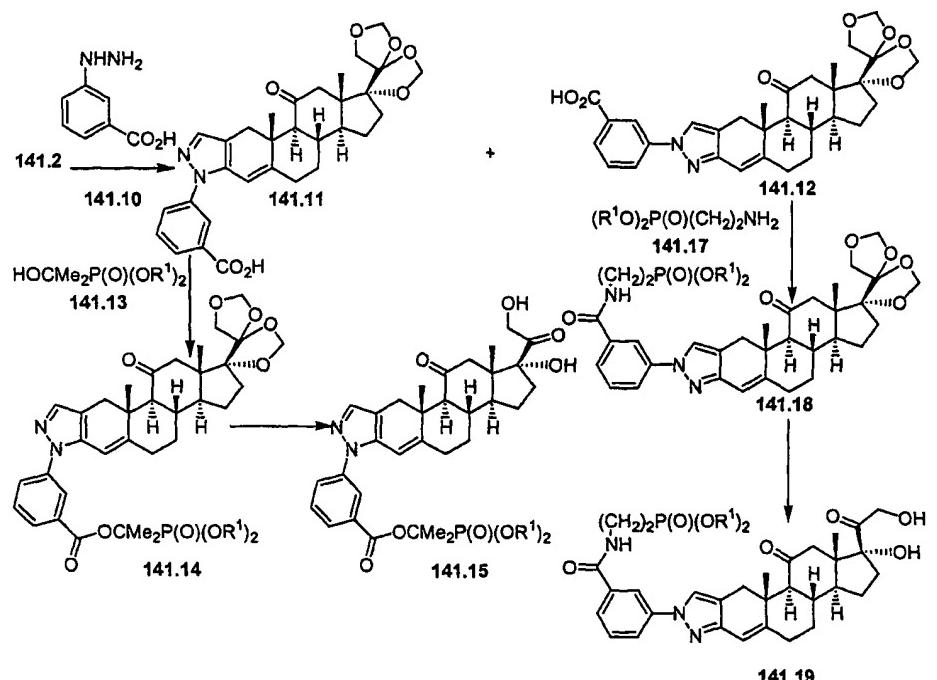
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Example 141 Preparation of Representative Prednisone Derivatives



10 The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above.. In this procedure, the BMD-protected dienone 139.2 is reduced to afford the 1,2-dihydro product 141.1. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, 1964, 86, 1520, to afford the 2-formyl product 141.2. This compound is then reacted
15 with an alkyl, aralkyl, aryl or heteroaryl hydrazine 141.3, in which the
20 with an alkyl, aralkyl, aryl or heteroaryl hydrazine 141.3, in which the

substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles 141.4 and 141.5. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The pyrazoles 141.4 and 141.5 are then transformed via the BMD-protected intermediates 141.6 and 141.7, into the phosphonates 141.8 and 141.9.



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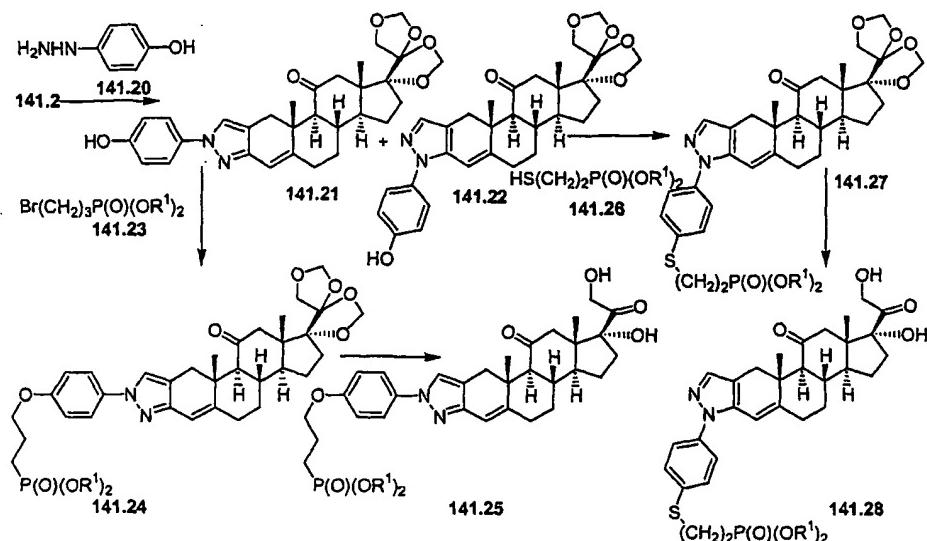
The preparation of phosphonates in which the phosphonate is attached by means of a phenyl ring and an ester or an amide linkage is illustrated above. In this procedure, the ketoaldehyde 141.2 is reacted, as described above, with 3-carboxyphenylhydrazine 141.10 (Apin) to give the pyrazoles 141.11 and 141.12. The 2'-substituted isomer 141.11 is then reacted in dichloromethane solution at ambient temperature with one molar equivalent of a dialkyl 2-hydroxy-2-methylpropyl phosphonate 141.13 (FR 2462440) and dicyclohexylcarbodiimide, to yield the ester 141.14. The protecting groups are then removed to yield the diol 141.15.

Alternatively, the 1'-substituted pyrazole 141.12 is coupled with a dialkyl 2-aminoethyl phosphonate 141.17 (Aurora) to afford the amide 141.18. The preparation of amides from carboxylic acids and derivatives is described, for example, in *Organic Functional Group Preparations*, by S.R.Sandler and W.

- 5 Karo, Academic Press, 1968, p. 274, and *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-
10 hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

- 15 Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. The product 141.18 is
20 then deprotected to give the diol 141.19.

- Using the above procedures, but employing different amino or hydroxyl-substituted phosphonates, and/or different carboxy-substituted hydrazines, the products analogous to 141.15 and 141.19 are obtained. The functionalization procedures are typically interchangeable between the pyrazole substrates 141.11
25 and 141.12.



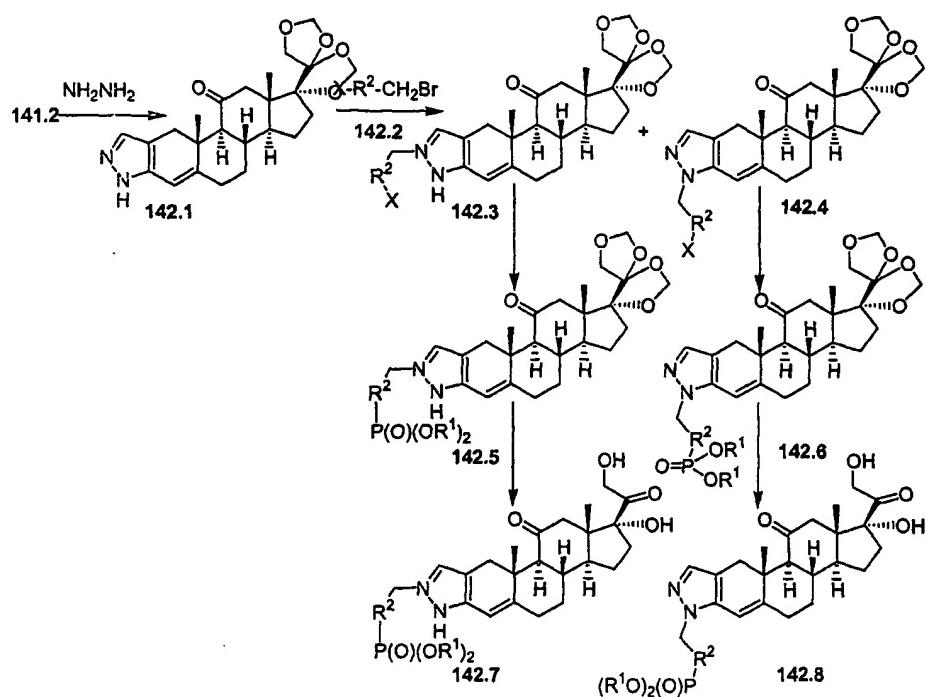
The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl group and an alkoxy or alkylthio carbon chain is illustrated above. In this procedure, the ketoaldehyde **141.2** is reacted, as

- 5 described above, with 4-hydroxyphenyl hydrazine **141.20** (EP 437105) to produce the pyrazoles **141.21** and **141.22**. The 1'-substituted isomer **141.21** is reacted, in dimethylformamide solution at 70°, with a dialkyl bromopropyl phosphonate **141.23** (J. Amer. Chem. Soc., 2000, 122, 1554) and potassium carbonate, to give the phosphonate **141.24**. The product is then deprotected to afford the diol **141.25**.

Alternatively, the 2'-substituted pyrazole **141.22** is reacted in a Mitsonobu reaction, as described above, with a dialkyl mercaptoethyl phosphonate **141.26** (Zh. Obschei. Khim., 1973, 43, 2364) to prepare the thioether phosphonate **141.27** which is deprotected to give the diol **141.28**.

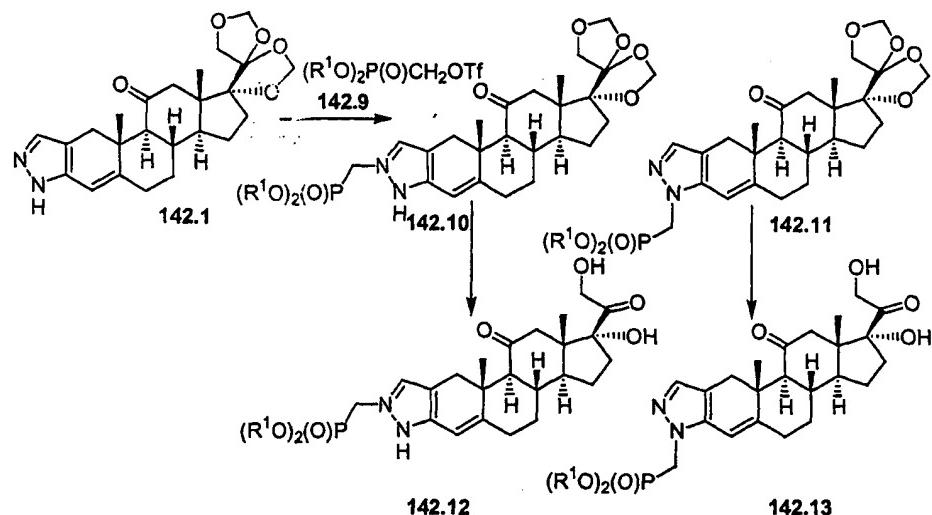
- 15 Using the above procedures, but employing, in place of the hydroxyphenyl reagent **141.20**, different hydroxy-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl bromo or mercapto-substituted phosphonates, the products analogous to the compounds **141.25** and **141.28** are obtained.

Example 142 Preparation of Representative Prednisone Derivatives



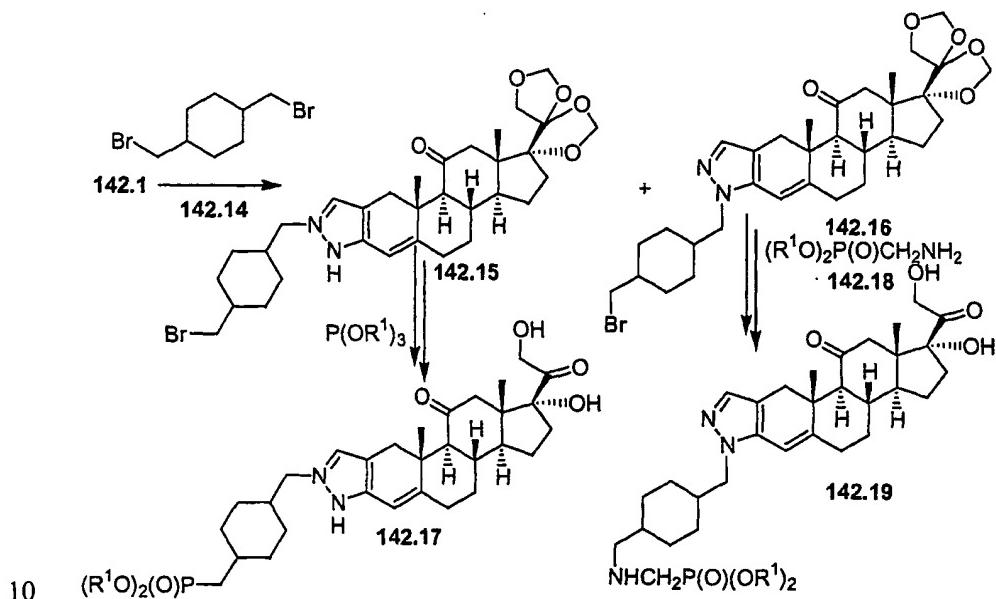
5 The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde 141.2 is reacted with hydrazine to afford the pyrazole derivative 142.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in J. Am. Chem. Soc., 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound 142.2, in which R^2 and X are as defined above, to yield the alkylation products 142.3 and 142.4. The alkylation of substituted pyrazoles is described, for example, in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products 142.3 and 142.4 are, except in cases where X is dialkylphosphono, converted

into the phosphonates 142.5 and 142.6, using the procedures described herein, and deprotection then affords the diols 142.7 and 142.8.



5

Representative compounds of the invention can be prepared as illustrated above. The pyrazole 142.1 is reacted with one molar equivalent of a dialkyl trifluoromethanesulfonyloxy phosphonate 142.9 to give the alkylated pyrazoles 142.10 and 142.11. Deprotection then yields the diols 142.12 and 142.13.



10

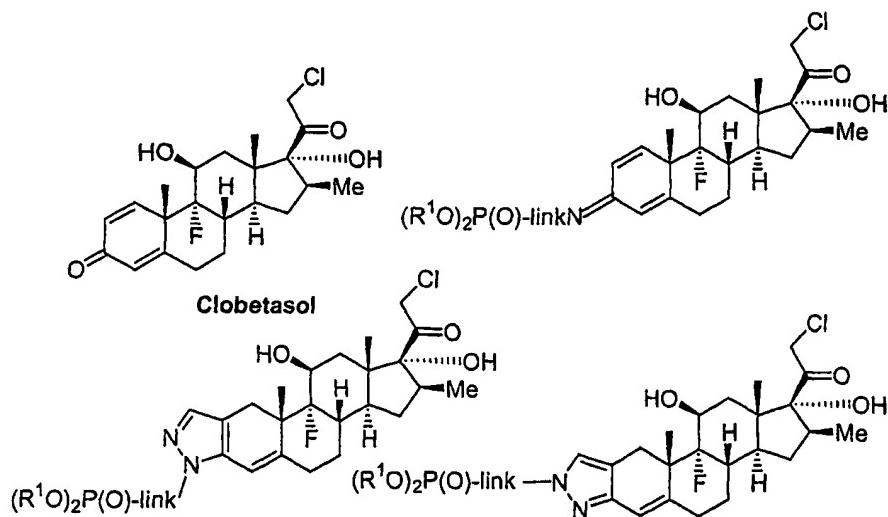
Representative compounds of the invention can be prepared as illustrated above. The pyrazole **142.1** is reacted, as described above, with 1,4-bis(bromomethyl)cyclohexane **142.14** (Salor) to give the pyrazoles **142.15** and **142.16**. The product **142.15** is subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain, the phosphonate **142.17**. The pyrazole **142.16** is reacted in dimethylformamide at 70° with potassium carbonate and a dialkyl aminomethyl phosphonate **142.18** (Interchim) to give after deprotection the amino phosphonate **142.19**.

Using the above procedures, but employing, in place of the dibromide **142.14**, different dibromides, and/or different amino-substituted phosphonates, the products analogous to **142.17** and **142.19** are obtained.

15

Examples 143-146 – Clobetasol Derivatives

The structures of clobetasol (US Patent 3721687) and representative phosphonate esters of the invention are shown below, in which the substituent R¹ is H, alkyl, alkenyl, aryl or aralkyl. These compounds incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.

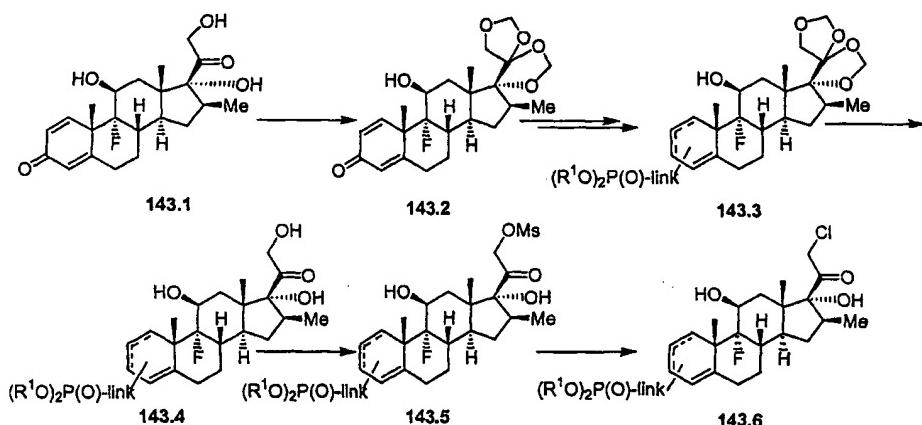


The synthesis of representative phosphonate derivatives of clobetasol is outlined in Examples 143-146. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards,

- 5 according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in
 10 Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 143 Preparation of Representative Clobetasol Derivatives

15

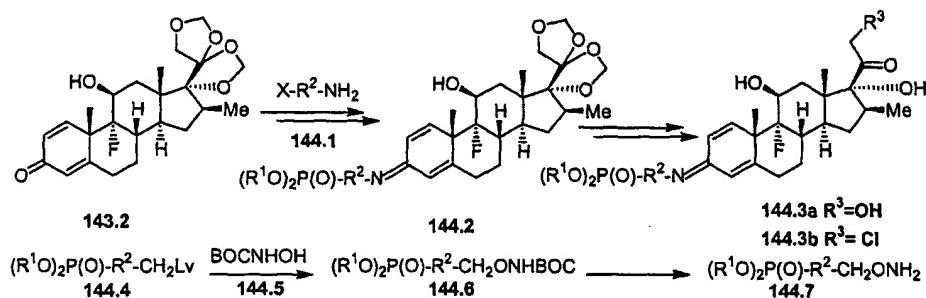


The preparation of representative compounds of the invention is illustrated above. The steroid side-chain is protected as a bis-methylenedioxy

- 20 (BMD) moiety. In this sequence, 9 α -fluoro-16 β -methyl-11 β ,17 α ,21-trihydroxypregn-1,4-dien-3,21-dione 143.1 (US patent 3721687) is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in
 25 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative 143.2. The phosphonate moiety is then introduced, using the procedures described below, to

produce the phosphonate ester **143.3**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol **143.4**. The 21-hydroxy group is then converted into the 21-chloro group as described in US Patent 3721687, Chimia, 1992, 46, 338, or *J. Med. Chem.*, 1987, 30, 1581. In this procedure, the 21-hydroxy substrate is reacted at about 0° with one molar equivalent of methanesulfonyl chloride in a basic solvent such as pyridine, to afford the 21-mesylate **143.5**. The product is then reacted, in dimethylformamide solution at about 70°, with ca. five molar equivalents of lithium chloride, to yield the 21-chloro product **143.6**.

Example 144 Preparation of Representative Clobetasol Derivatives



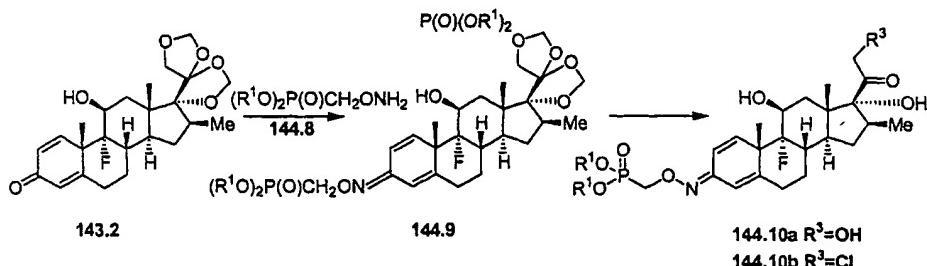
15

The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative **143.2** is reacted with an amine or hydroxylamine **144.1**, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol,

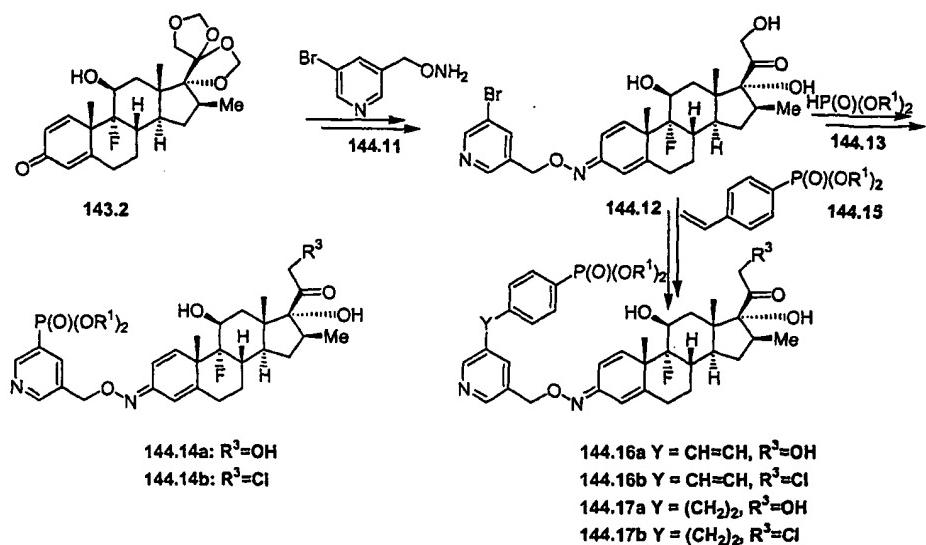
optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, 1978, 86, 133. and in *J. Mass. Spectrom.*, 1995, 30, 497. The BMD-protected side-chain compound 144.2 is then converted into the triol 144.3a, and then to the 21-chloro product 144.3b.

The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate 144.4, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 144.5 (Aldrich) to produce the ether 144.6. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 144.7.

15



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate 143.2 is reacted with a dialkyl phosphonomethyl hydroxylamine 144.8, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tet. Lett.*, 1986, 27, 1477) and BOC-hydroxylamine, to afford the oxime 144.9. Deprotection then affords the triol 144.10a from which the 21-chloro compound 144.10b is prepared. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants. Using the above procedures, but employing, in place of the hydroxylamine ether 144.8, different oxime ethers 144.1, the corresponding products 144.3b are obtained.



The preparation of compounds in which the phosphonate group is attached by means of a 3-pyridylmethoxy oxime group is illustrated above. In this procedure, the dienone 143.2 is reacted, as described above, with O-(5-bromo-3-pyridylmethoxy)hydroxylamine 144.11, prepared as described above from 5-bromo-3-bromomethylpyridine (WO 9528400) and BOC-protected hydroxylamine, to give, after deprotection of the side-chain, the oxime 144.12.

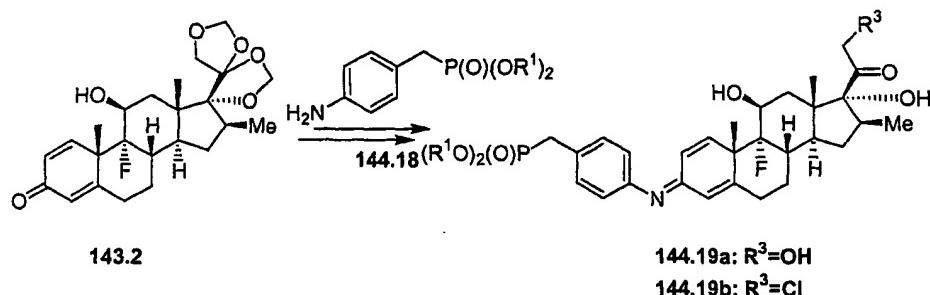
- 5 The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite 144.13 to afford the phosphonate 144.14a. The preparation of 10 arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)-15 palladium(0). The 21-hydroxy group is then converted into the 21-chloro derivative 144.14b.

Alternatively, the bromo compound 144.12 is coupled with a dialkyl 4-vinylphenyl phosphonate 144.15 (Macromolecules, 1998, 31, 2918) to afford the phosphonate 144.16a. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. 20 A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst

such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 144.16a is reduced, for example by reaction with diimide.

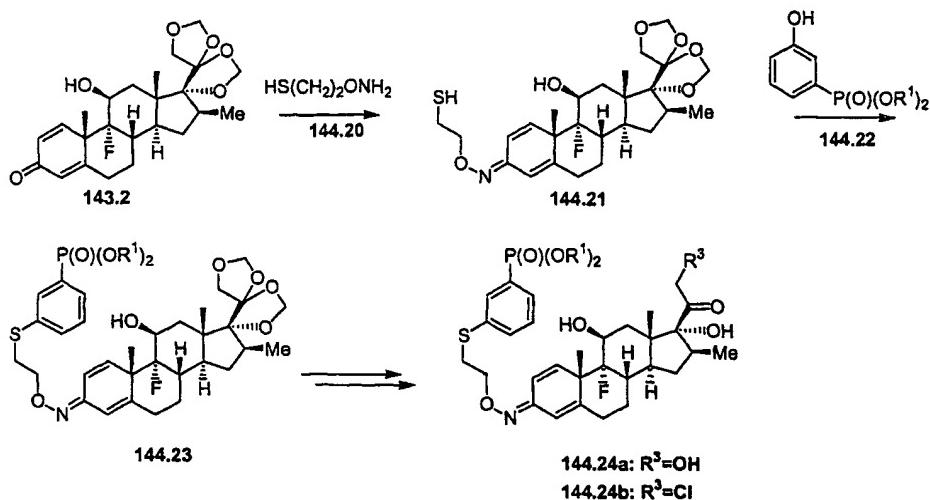
- 5 to produce the saturated analog 144.17a. The reduction of olefinic bonds is
described in Comprehensive Organic Transformations, by R. C. Larock, VCH,
1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation,
for example using a palladium on carbon catalyst and hydrogen or a hydrogen
donor, or by the use of diimide or diborane. The products 144.16a and 144.17a
10 are then converted into the 21-chloro analogs 144.16b and 144.17b.

Using the above procedures, but employing, in place of the bromopyridylmethoxy reagent **144.11**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds **144.14b**, **144.16b** and **144.17b** are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate 143.2 is reacted with a dialkyl 4-aminobenzyl phosphonate 144.18, (Fluka) to give, after deprotection, the imine product 144.19a. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. The product is then converted into the 21-chloro compound 144.19b. Using the above procedures, but employing, in place of the 4-aminobenzyl phosphonate 144.18 different

amino-substituted aryl or heteroaryl phosphonates, products analogous to **144.19b** are obtained.



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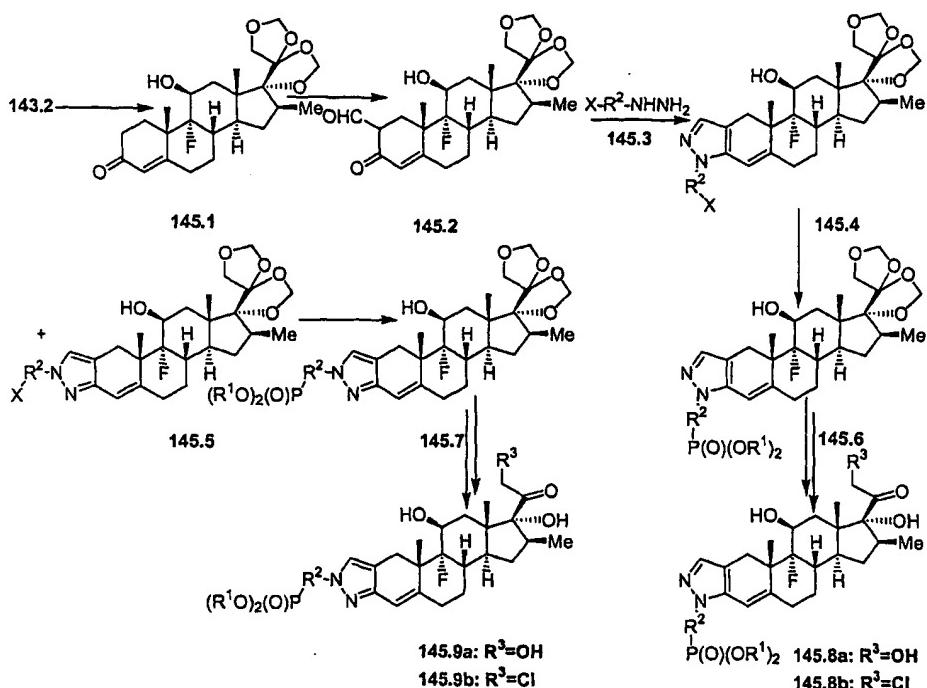
The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and a thioether linkage is illustrated above. In this procedure, the dienone **143.2** is reacted with O-(2-mercaptopethyl)hydroxylamine **144.20** (*Bioorganicheskaya Khim.*, 1986, 12, 1662) to yield the oxime **144.21**.

- 10 The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, 1976, 7, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product is then coupled, in a Mitsonobu reaction, with a dialkyl 3-
- 15 hydroxyphenyl phosphonate **144.22** (Aurora), to yield the thioether oxime **144.23**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 448, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in *Org. React.*, 1992,
- 20 42, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, 1992, 42, 335-656.

The thioether product **144.23** is then converted into the 21-chloro product **144.24b**.

Using the above procedures, but employing, in place of the hydroxylamine **144.22**, different hydroxy or mercapto-substituted hydroxylamines, and/or different hydroxyaryl-substituted phosphonates, the products analogous to **144.24b** are obtained.

Example 145 Preparation of Representative Clobetasol Derivatives

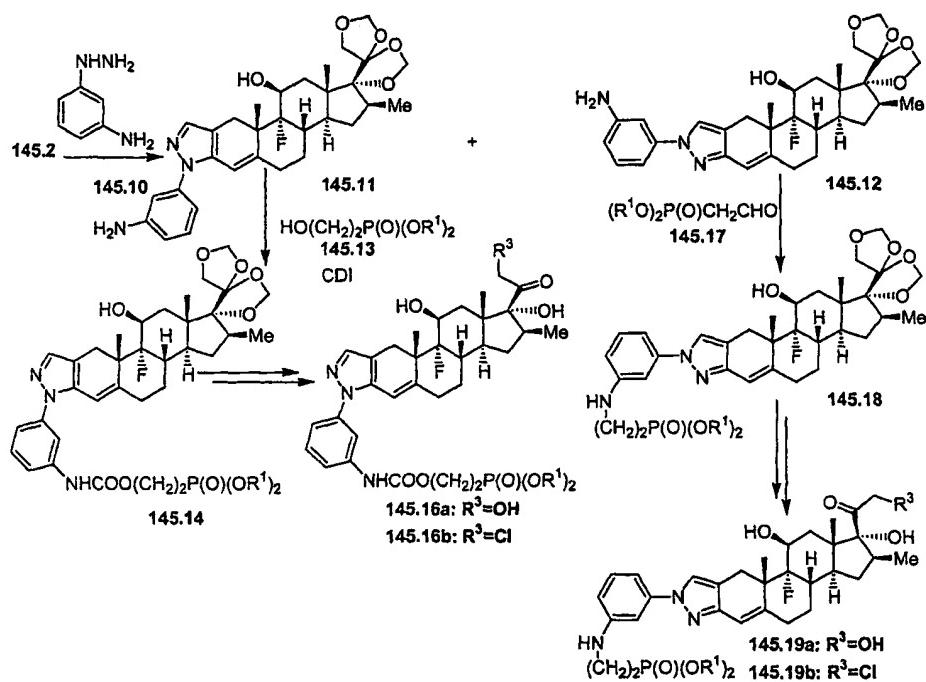


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The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, the BMD-protected dienone **143.2** is reduced to afford the 1,2-dihydro product **145.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, 1964, 86,

1520, to afford the 2-formyl product **145.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine **145.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono,

- 5 bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles **145.4** and **145.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The pyrazoles **145.4** and **145.5** are then transformed, via the BMD-protected intermediates
- 10 **145.6** and **145.7**, into the 21-chloro phosphonates **145.8b** and **145.9b**.

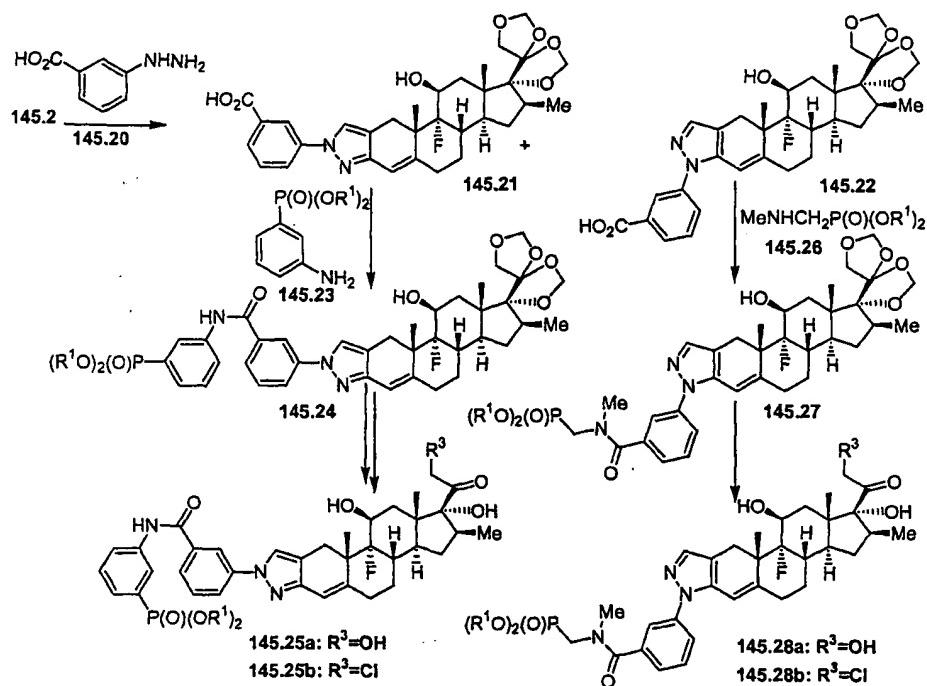


- The preparation of phosphonates in which the phosphonate is attached by means of a carbamate or an amino linkage is illustrated above. In this procedure, the ketoaldehyde **145.2** is reacted, as described above, with 3-aminophenylhydrazine **145.10** (EP 437105) to give the pyrazoles **145.11** and **145.12**. The 2'-substituted isomer **145.11** is then reacted in dimethylformamide solution at ambient temperature with one molar equivalent of a dialkyl 2-hydroxyethyl phosphonate **145.13** (Epsilon) and carbonyl diimidazole, to yield the carbamate
- 15 **145.16a**: $\text{R}^3 = \text{OH}$
145.16b: $\text{R}^3 = \text{Cl}$
- 20 **145.19a**: $\text{R}^3 = \text{OH}$
145.19b: $\text{R}^3 = \text{Cl}$

145.14. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff. In the procedure, the amine is reacted 5 in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate. The BMD protecting group is then removed and 10 the product is converted into the 21-chloro product 145.16b.

Alternatively, the 1'-substituted pyrazole 145.12 is reacted, in a reductive amination reaction, with a dialkyl formylmethyl phosphonate 145.17 (*Zh. Obschei. Khim.*, 1987, 57, 2793) and sodium triacetoxyborohydride, to afford the amine 145.18. The preparation of amines by means of reductive amination 15 procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, 20 borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The product 145.18 is then deprotected to give the triol 145.19a, and the latter compound is transformed into the 21-chloro analog 145.19b.

25 Using the above procedures, but employing different formyl or hydroxyl-substituted phosphonates, and/or different amino-substituted hydrazines, the products analogous to 145.16b and 145.19b are obtained. The functionalization procedures are typically interchangeable between the pyrazole substrates 145.11 and 145.12.



The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl ring and an amide linkage is illustrated above. In
 5 this procedure, the ketoaldehyde 145.2 is reacted, as described above, with 3-
 carboxyphenyl hydrazine 145.20 (Apin) to produce the pyrazoles 145.21 and
 145.22. The 1'-substituted isomer 145.21 is coupled, in the presence of
 dicyclohexylcarbodiimide, with a dialkyl 3-aminophenyl phosphonate 145.23
 (Aurora) to give the amide 145.24. The preparation of amides from carboxylic
 10 acids and derivatives is described, for example, in Organic Functional Group
 Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and
 Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p.
 972ff. The carboxylic acid is reacted with the amine in the presence of an
 activating agent, such as, for example, dicyclohexylcarbodiimide or
 15 diisopropylcarbodiimide, optionally in the presence of, for example,
 hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-
 protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford
 the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

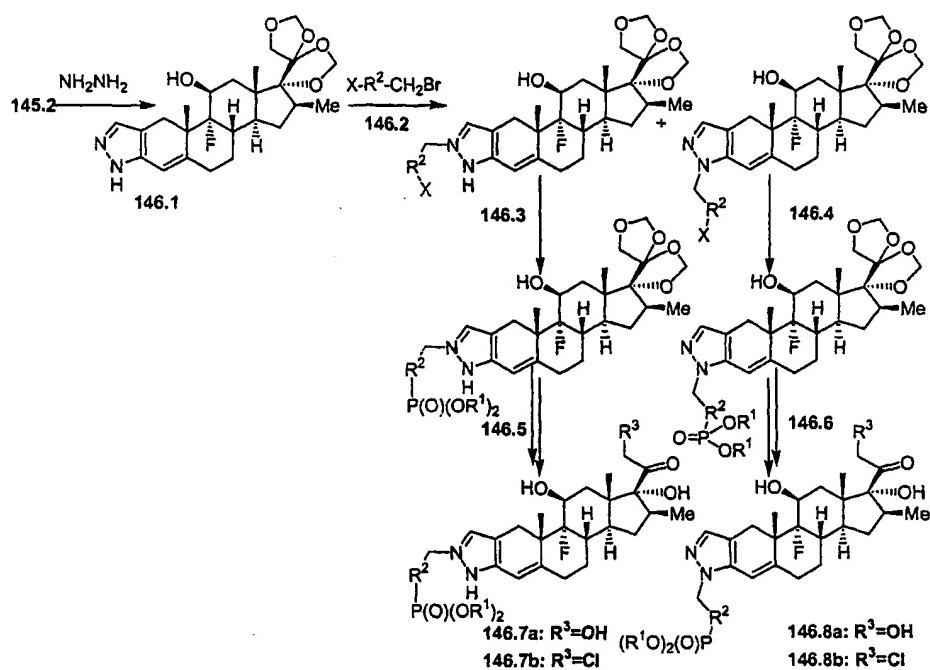
5 The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. The product is then deprotected to afford the triol 145.25a
10 which is converted into the 21-chloro compound 145.25b.

Alternatively, the 2'-substituted pyrazole 145.22 is coupled, as described above, with a dialkyl methylaminomethyl phosphonate 145.26 (AsInEx) to prepare the amide phosphonate 145.27 which is deprotected, and the product is converted into the 21-chloro analog 145.28b.

15 Using the above procedures, but employing, in place of the carboxyphenyl hydrazine 145.20, different carboxy-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl amino-substituted phosphonates, the products analogous to the compounds 145.25b and 145.28b are obtained.

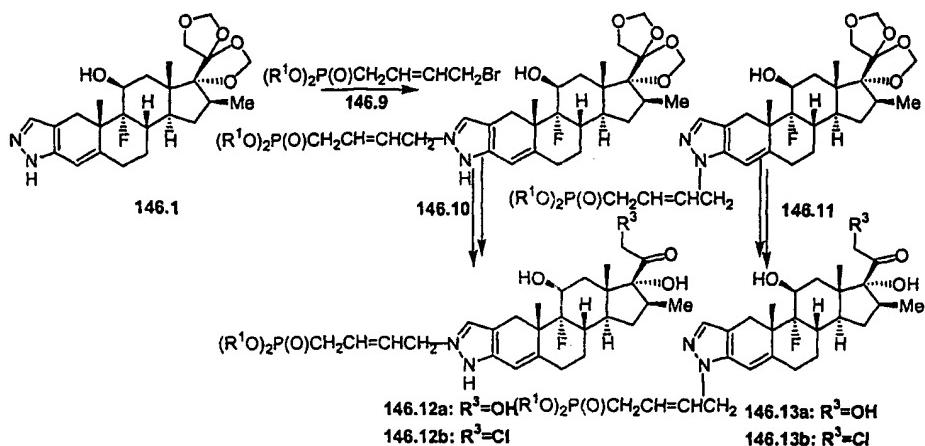
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Example 146 Preparation of Representative Clobetasol Derivatives



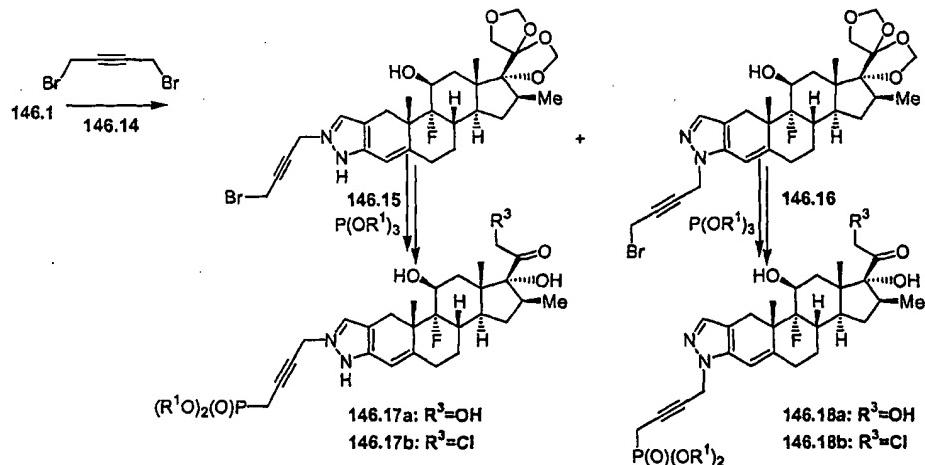
The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde **145.2** is reacted with hydrazine, to afford the

- 5 pyrazole derivative **146.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound **146.2**, in which R^2 and X are as defined above, to yield the alkylation products **146.3** and **146.4**. The alkylation of
- 10 substituted pyrazoles is described, for example, in *Heterocyclic Chemistry*, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products
- 15 **146.3** and **146.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates **146.5** and **146.6**, using the procedures described herein, and deprotection/acylation then affords the 21-chloro compounds **146.7b** and **146.8b**.



The preparation of representative compounds of the invention is illustrated above. The pyrazole 146.1 is reacted in tetrahydrofuran solution, as described above, with one molar equivalent of a dialkyl bromobutenyl phosphonate 146.9 (*J. Med. Chem.*, 1992, 35, 1371) and lithium hexamethyldisilazide to give the alkylated pyrazoles 146.10 and 146.11. Deprotection/chlorination then yields the 21-chloro products 146.12b and 146.13b.

10



The preparation of representative compounds of the invention is illustrated above. The pyrazole 146.1 is reacted in tetrahydrofuran solution, as described above, with 1,4-dibromobut-2-yne 146.14 (Aldrich) to give the pyrazoles 146.15 and 146.16. The products are subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl